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NUTRITION AND BONE DISEASE*

RICHARD H. FOLLIS, JR., M.D.

*Department of Pathology, Johns Hopkins University School of Medicine
Baltimore, Md.*

Cartilage and bone are too frequently looked upon as static tissues; the reverse is, of course, true, particularly during the phase of most active growth in the animal organism. Because cartilage and bone require certain essential nutrients for normal growth, profound alterations may readily be produced in such tissues of laboratory animals by withholding one or more of the known dietary essentials. The occurrence of similar lesions in the human, especially in children during the critical period of maximal growth, is therefore not surprising. In this country, at least, nutritional disease in man manifests itself clinically and at autopsy more often in the skeleton than in any other tissue of the body; moreover, the actively growing bones of the child are much more likely to be involved than those of the adult (1).

In order to understand the pathogenesis of the bone lesions shortly to be discussed it will be advantageous to review briefly certain fundamentals of normal bone growth. We recognize two types of osseous development: membranous and endochondral (fig. 1). The first, which is found primarily in certain of the skull bones, is characterized by the differentiation of mesenchymal cells into osteoblasts, the elaboration of an organic intercellular matrix by these cells and the deposition of inorganic elements in this matrix to form true bone. The second type, which concerns us more than does the foregoing, is based upon the transformation of plates of cartilage into bone by invasion of the cartilage by cells and blood vessels. Early in embryonal life, if we take a limb bud as an example, aggregates of mesenchymal cells proliferate and differentiate into cartilage cells. As a result of this multiplication and maturation a mass of cartilage having striking similarity to the form of the final bone is found (fig. 2). In the center of this plate of cartilage appears an area where ossification is to begin; here large vesicular cells imbedded in an organic matrix are found. At the same time cells about the nearby periphery of the cartilage begin to produce organic matrix in which inorganic materials are deposited; that is, periosteal bone formation commences. The central zone is soon invaded by mesenchymal cells and blood vessels which begin the process of endochondral bone formation (fig. 3). If we take the costo-chondral junction, an area most easily available at autopsy, as the prototype, one can separate events into several phases (figs. 4 and 5). First, one finds varying degrees of differentiation of the cartilage cells. High up in the cartilage the cells are small and undifferentiated; as one approaches the shaft they grow larger and arrange themselves into rows. As the

* A part of the experimental work cited herein has been aided by a grant from Mead Johnson and Company.

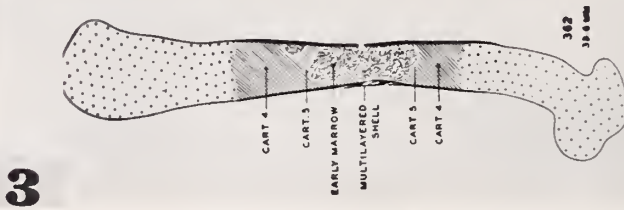
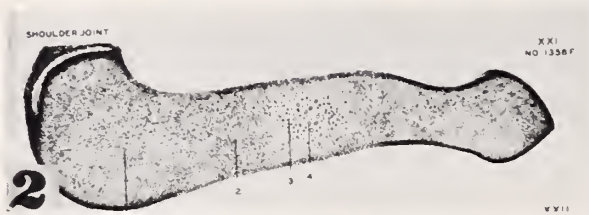
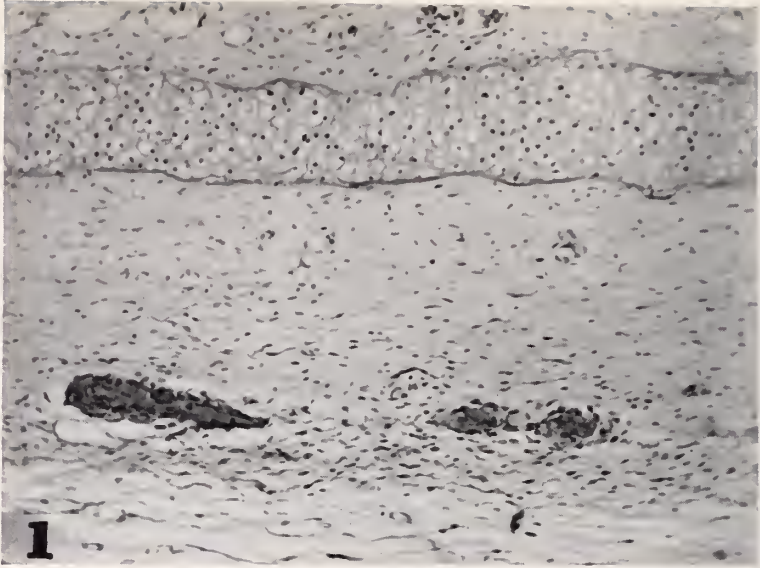


FIG. 1. Sections from skull of 3 months fetus to show membranous and endochondral bone formation going on side by side. There are two foci of the former type in the lower part of the field; a plate of cartilage, not yet surrounded by a collar of bone or invaded by blood vessels lies across the upper portion of the field.

FIG. 2. Cartilage plate from which the humerus will develop. Note general contour which is reminiscent of the final shape. The cells in the center are becoming larger and being prepared for bone formation. (From G. L. Streeter, (13), Courtesy, Carnegie Institute of Washington.)

FIG. 3. Schematic presentation of the developing humerus after invasion by cells and blood vessels and the formation of a definitive marrow cavity. The external contour resembles even more the final shape of the adult bone. (From G. L. Streeter, (13), Courtesy of Carnegie Institute of Washington.)

cartilage-shaft junction is reached the cells have become extremely large with clear cytoplasm. In the matrix between these rows of hypertrophic cells a

second important phase occurs—inorganic materials, particularly calcium, phosphorus and carbonate, are being deposited, and show up in properly prepared sections as dark-blue staining areas (fig. 5). In this region, too, a third important mechanism is observed—blood capillaries grow up to erode and destroy the cartilage cell columns. This leaves a scaffolding of bare inorganic impregnated matrix upon which as a framework osteoblasts can deposit osteoid,

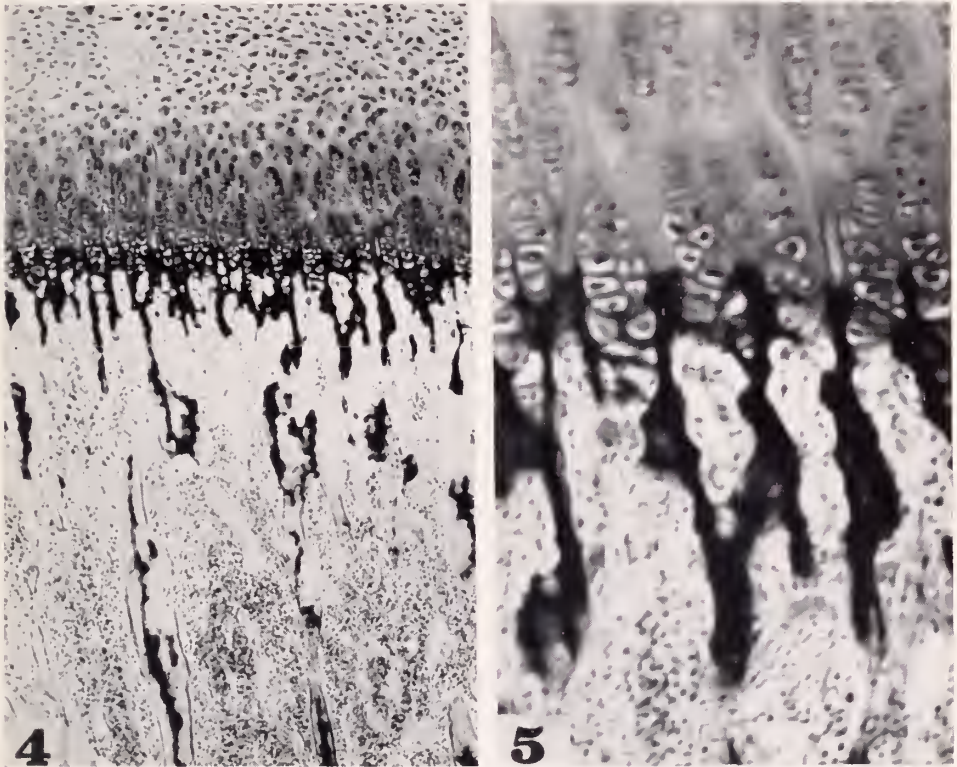
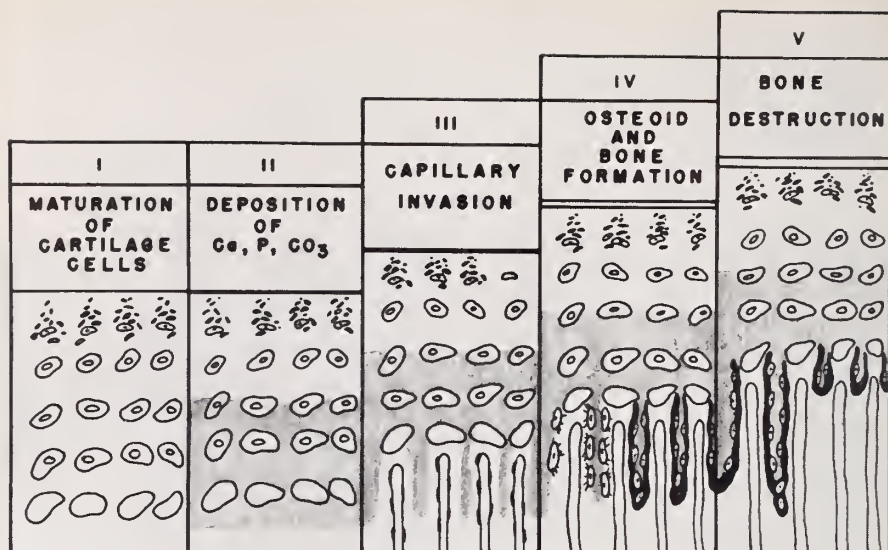


FIG. 4. Low power magnification of section of costochondral junction from a 6 months old child. Note zone of small, undifferentiated cartilage cells above; they increase in size as the cartilage-shaft junction is reached. The black material in this region represents cartilage matrix in which inorganic materials: calcium, phosphorus, carbonate, etc. are deposited. Note remnants of matrix encased in bone down in the shaft.

FIG. 5. Higher power of Figure 4 to show details at cartilage shaft junction.

the organic structure of bone. Minerals (calcium, phosphorus, carbonate, etc.) are immediately deposited in this material and true bone is thus formed. If the greater part of such matrix encased in bone were not quickly destroyed, the rib or any other bone would become inordinately dense. Immediately, therefore, a large part of this material is eliminated. We can thus visualize such endochondral bone formation in a series of stages as depicted in figure 6, all, of course, going on simultaneously.

From this brief review of normal osteogenesis we can separate bone growth into three main categories: 1) growth of cartilage, 2) maintenance of proper



6

FIG. 6. A schematic breakdown of the events in endochondral bone formation.

TABLE I
A classification of bone disease

I. Disturbance in Growth of Cartilage	
1) Increased Activity	a) Hyperpituitarism, b) Hyperthyroidism
2) Decreased Activity	a) Inanition, b) Hypopituitarism, c) Hypothyroidism, d) Achondroplasia
II. Disturbance in Osteogenic-osteolytic Balance:	
1) Decreased Osteoblastic Activity:	a) Inanition and disuse, b) Hypopituitarism, c) Hypothyroidism, d) Ascorbic acid deficiency, 3) Osteogenesis imperfecta, f) Post-menopausal osteoporosis, g) Cushing's Syndrome
2) Increased Osteoblastic Activity:	a) Increased local activity and blood supply, b) Acromegaly, c) Androgenic stimulation (?), d) Hyperestrogenism (mouse), e) Hypertrophic osteoarthropathy
3) Decreased Osteolytic Activity:	a) Marble bone disease, b) Hyperestrogenism (rat)
4) Increased Osteolytic Activity:	a) Acute severe inanition, b) Disturbance in serum Ca and/or P. (hyperparathyroidism, hypervitaminosis D, nephritis, acidosis), c) Paget's disease, d) Hypervitaminosis A.
III. Disturbance in Deposition of Inorganic Elements in Cartilage Matrix and/or Osteoid.	
1) Defective Ca and/or P. (Rickets, osteomalacia)	
2) Excessive Pb, Bi, Sr.	

osteoblastic-osteolytic balance, 3) deposition of calcium, phosphorus, carbonate and other inorganic elements in cartilage matrix and/or osteoid. On this basis one can formulate a satisfactory classification of bone disease with similar headings: 1) disturbance in growth of cartilage (increased or decreased activity), 2) disturbance in the normal osteoblastic-osteolytic balance, 3) disturbance in the deposition of inorganic elements in cartilage matrix and/or osteoid. Such a classification of bone disease, excluding inflammatory processes and tumors, is presented in the accompanying Table I, where it may be noted that those listed fit rather well into the various categories if one bears in mind that each disease is classified under its primary cause factor and that secondary factors may, as, for instance, in Paget's disease, be more predominant. All these, of course, represent metabolic disturbances of cartilage and bone of known and unknown etiology. Because of time limitation, I cannot discuss each one but shall limit myself to a discussion of the diseases produced by deficiencies of dietary factors, taking an example from each of the three main categories.

The commonest change which one finds in experimental animals and in the human, too, is a non-specific one, affecting the growth of both cartilage and bone, as well as virtually all of the other tissues in the organism (2). This change has been termed inanition or *athrepsia*. The reason one uses the term "non-specific" is that the characteristic changes encountered may be produced in experimental animals by withholding from the diet one or more of most of the forty-odd essential nutrients: elements, amino acids, vitamins and fatty acids. We have, for instance, observed such changes as a result of a deficiency of potassium (3), zinc (4), sodium (5) or iron (6). Interference with the intake of protein (6), carbohydrate (6) or merely calories (7) may also lead to similar disturbances. So too, restriction in the diet of the various members of the water soluble group of vitamins has a profound effect on the growth of cartilage and bone. Characteristic changes in an experimental animal, in this instance on a protein deficient diet, are shown in figure 7 and are obvious enough when compared with the normal control (fig. 8). It will be noted that there is a decided diminution in the width of the epiphyseal plate of cartilage. The rows of cartilage cells are much shorter, all stages in the development of the cells being affected. As a result there is virtually complete cessation of growth of the bone in length. In addition, as will be noted at the cartilage-shaft junction, there is very little cartilage matrix, and on what there is, little bone has been or is being deposited. In the shaft as well, one finds relatively few osteoblasts about trabeculae. One would find the cortex narrower than the normal. The example which we have chosen to reproduce is obviously an extreme one. However, it is not hard to visualize changes of lesser degree which one might expect to encounter under circumstances less stringent than those produced in the laboratory. Such alterations (figs. 9 and 10) are seen in children as a result of disease and malnutrition and resemble those observed in experimental animals. The effects of inanition in the human are, of course, due to multiple deficiencies of essential nutrients and calories. The widespread skeletal disturbances following both World Wars in Europe undoubtedly had such changes in growth of cartilage and bone as their basis.

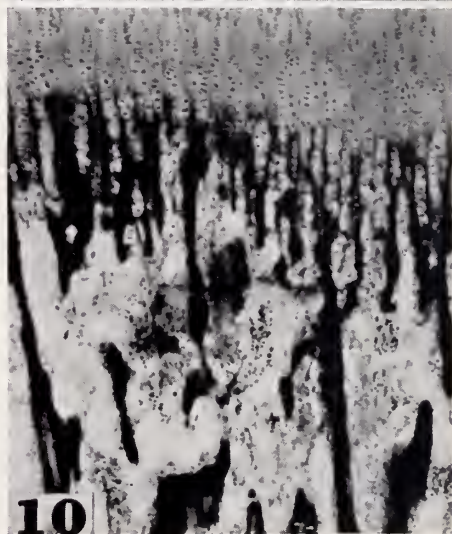
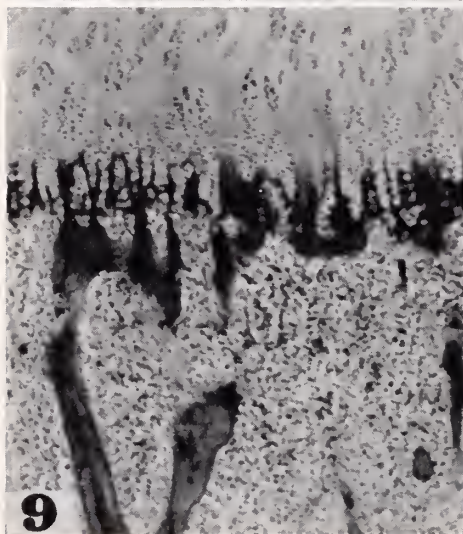
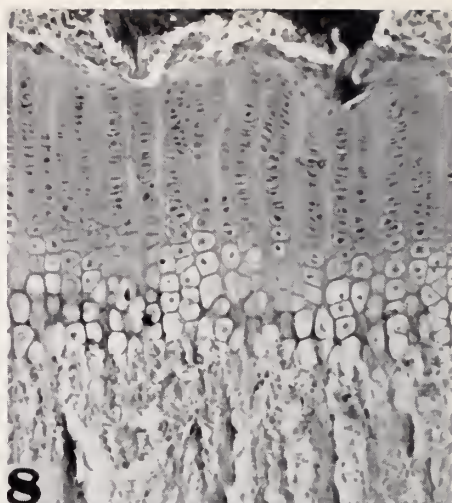


FIG. 7. Epiphyseal cartilage of upper end of tibia of young rat which had been placed on a diet completely deficient in protein but adequate in all other known nutrients for 10 days. Compare with figure 8.

FIG. 8. Upper end of tibia at same magnification from litter mate of animal shown in figure 7.

FIG. 9. Costochondral junction from 2 month old infant dying of bacillary dysentery of three weeks duration. Note decrease in width of zone of hypertrophic cartilage cells, diminution in calcified matrix of the cartilage and bone in the shaft. Compare with figure 10 (same magnification).

FIG. 10. Costochondral junction from a 2 months old infant dying acutely of otitis media and longitudinal sinus thrombosis. The zone of ossification is normal in appearance. This is the same magnification as the section shown in figure 9.

In addition to these non-specific changes produced by restriction of calories and the various essential nutrients in man, we must turn to two very specific nutritional diseases of the skeleton: scurvy and rickets, which may appear

singly or together and which, naturally, are frequently accompanied by evidence of inanition.

Scurvy may be defined for our purposes as that disease which results from a deficiency of ascorbic acid in the tissues and which is characterized by a disturbance in the formation of collagen, dentine and osteoid by their respective cells. We shall be concerned with the last of these so called intercellular substances, osteoid, the organic component of bone. In scurvy, whether in the susceptible guinea pig or in man, there is no seeming disturbance in the growth of cartilage (at least until late in the disease). Cartilage cells proliferate and line up in rows; inorganic elements are deposited in the matrix between the

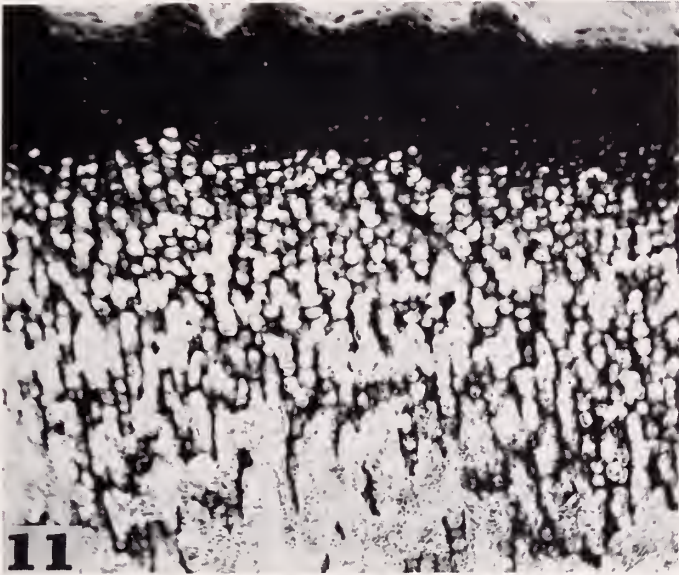


FIG. 11. "Synthetic" scurvy. Upper end of tibia of scorbutic guinea pig whose leg had been placed in a cast. Cartilage is normal. There is a broad zone of calcified cartilaginous matrix which is neither being destroyed or encased in osteoid (and bone).

rows, and blood vessels invade the cell columns in normal fashion. Here, however, the similarity to normal endochondral bone formation ends (fig. 11). Osteoblasts fail to deposit osteoid on the calcified matrix framework or on the already formed trabeculae in the shaft. This cessation of osteoblastic activity is the basic principle in the pathogenesis of the skeletal lesions of scurvy. The presence of the broad zone of cartilage matrix, impregnated with organic materials but not destroyed or encased in strengthening bone by impotent osteoblasts, results in a weakened area which, because of respiratory movements in the case of the ribs or muscle pull and weight bearing in the case of the extremities, leads to fractures of the matrix in this region. Herein result separation of the cartilage from the shaft, hemorrhage in this area and beneath the adjacent periosteum and the entire classical histological picture of scurvy with *Trümmerfeldzone*, *Gerüstmark*, etc. (figs. 12 and 14). The importance of mechanical

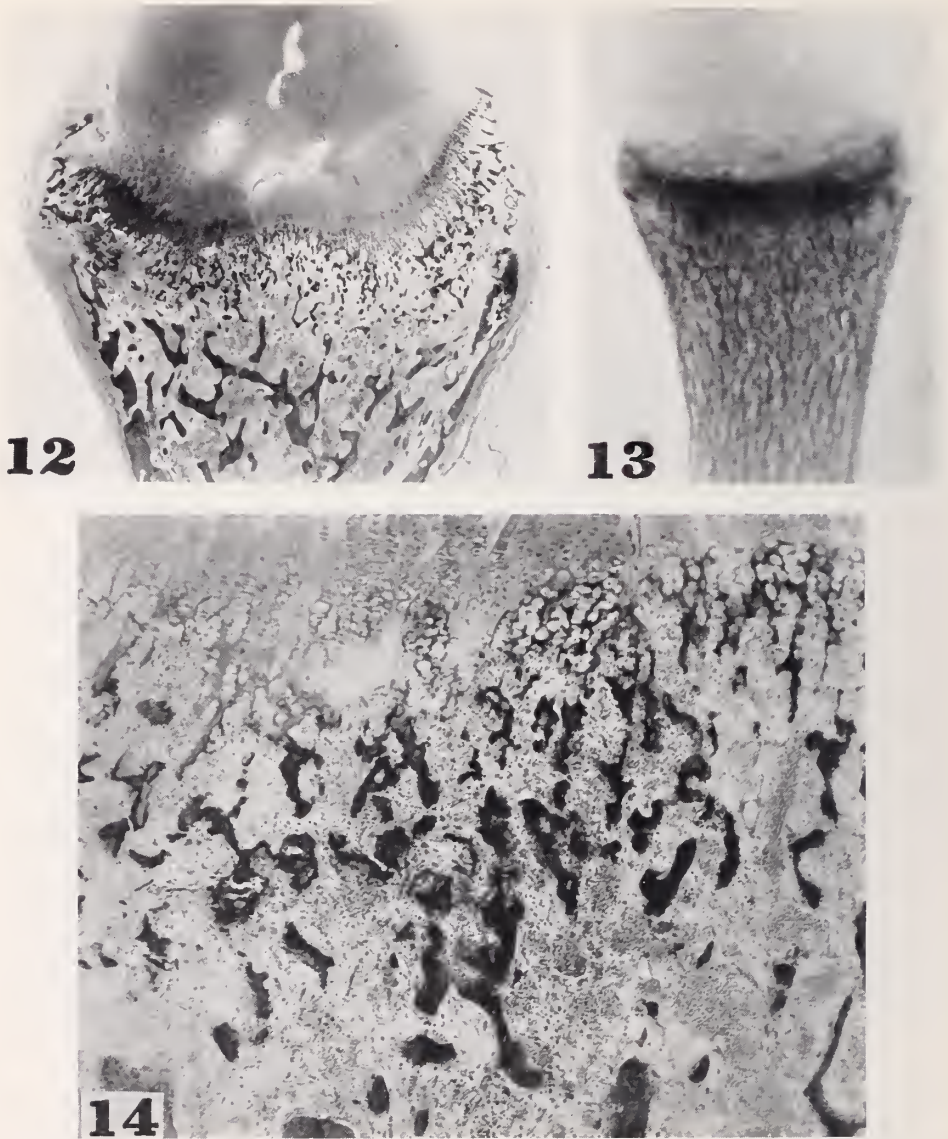


FIG. 12. Costochondral junction from a 6 months old child dying of dysentery after an illness of 8 days. The baby had never received orange juice. Note widening of the line of ossification with characteristic concavity of the shaft. There are numerous fractures. (From *The Pathology of Nutritional Disease* by Richard H. Follis, Jr., M.D. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

FIG. 13. X-ray (positive print) of rib shown in figure 12. Note convexity of cartilage. Particularly prominent is the dark zone (bright in x-ray film) between cartilage and shaft. This represents the area of fractured, persisting spicules of calcified cartilaginous matrix.

FIG. 14. High power of cartilage shaft junction of rib shown in figure 12. Note fragments of calcified cartilaginous matrix lying in all directions and unencased in bone. The marrow is cellular yet contains no myeloid elements. There is very little evidence of healing. (From *The Pathology of Nutritional Disease* by Richard H. Follis, Jr., M.D. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

factors may be illustrated by an experiment (8) on a scorbutic guinea pig; the marked difference between a hind limb immobilized in a plaster cast and the opposite one allowed to bear weight can readily be seen in figures 15 and 16.

In children scurvy is observed almost entirely during the first year of life, rarely thereafter. In a study (9) reported several years ago morphological evidence of scurvy was found in 11.7 per cent of children between 3 and 19 months of age coming to autopsy in the Johns Hopkins Hospital. Ascorbic acid deficiency is therefore important as a cause of nutritional disease in young

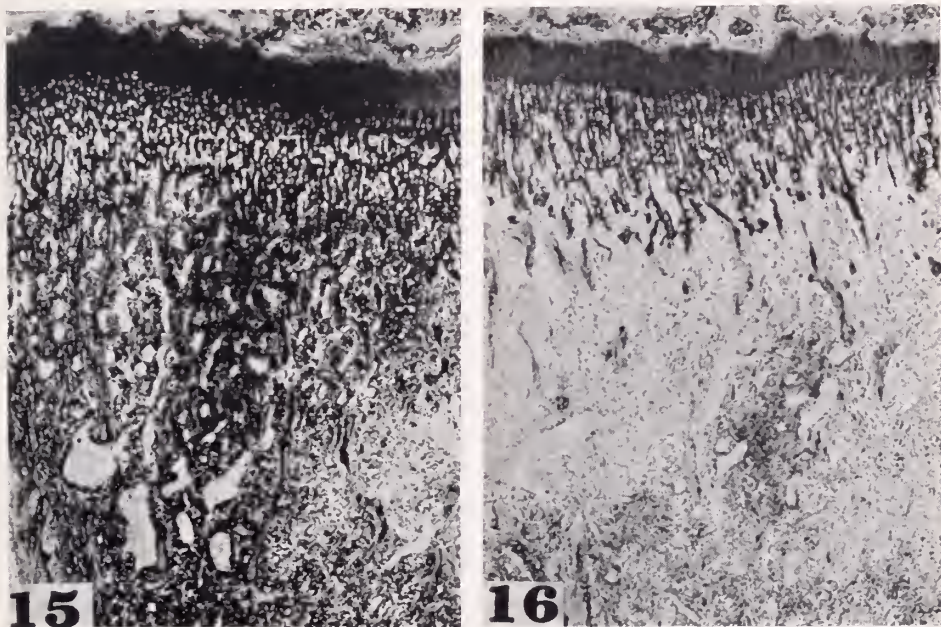


FIG. 15. Upper tibia of guinea pig which had been placed in a plaster cast before the onset of acute scurvy. Note dense zone of bare calcified cartilaginous matrix. Osteoblasts are unable to lay down osteoid on this material or destroy it.

FIG. 16. Opposite tibia to that shown in figure 15. This limb had been allowed free motion. The section shows the classical characteristics of skeletal scurvy: fractures of the calcified matrix, fibrous marrow, disappearance of marrow cells, etc. (Figures 15 and 16 from *The Pathology of Nutritional Disease* by Richard H. Follis, Jr., M.D. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

children. Such evidence based on strict morphological criteria is certainly the most exact that one can hope to obtain at this time. It is unfortunate that correlation studies with tissue and blood level concentrations of ascorbic acid are not available to place tests for clinical evaluation of Vitamin C deficiency in proper perspective.

Park and his collaborators (10) and others have pointed out that when scurvy is present in advanced enough degree its effects may be beautifully demonstrated by x-ray examination. Figure 13 shows the roentgenographic appearance of the section shown in figure 12; the reasons for the x-ray changes are clearly recognized; the concave shaft and convex cartilage, the widening of the cartilage-

shaft junction, the zone of increased density as a result of excess cartilage matrix and the underlying zone of decreased density, all are shown and can be compared with what one observes in the section.

A more common nutritional bone disease than scurvy and one which is also encountered in children is rickets. Rickets may be defined as a disturbance in the normal deposition of inorganic materials, principally calcium and phosphorus, in cartilage matrix and/or osteoid. The disturbance results from an alteration in the serum concentrations of calcium and phosphorus. In experi-

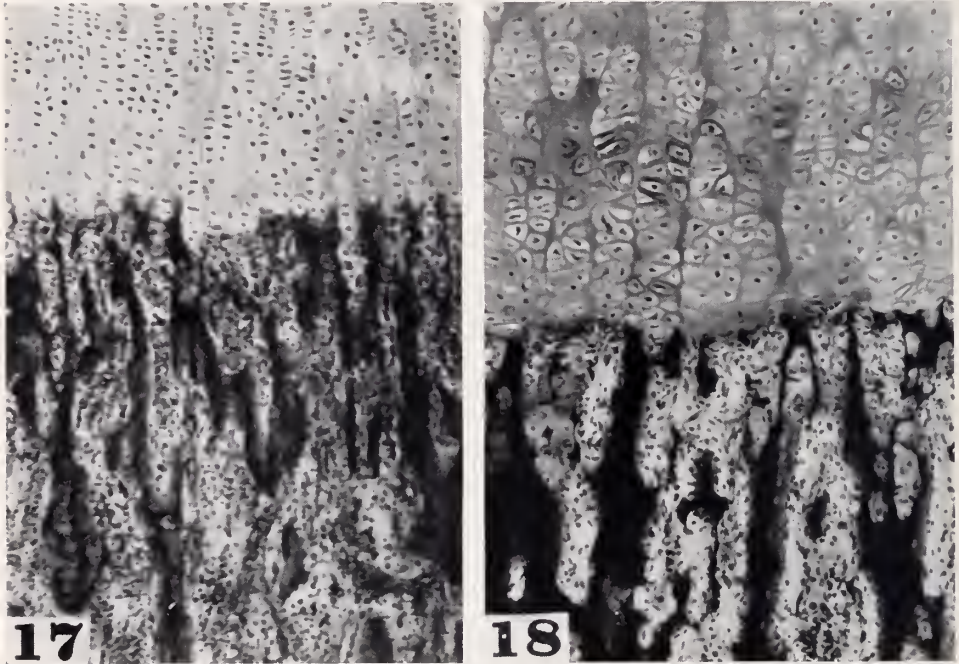


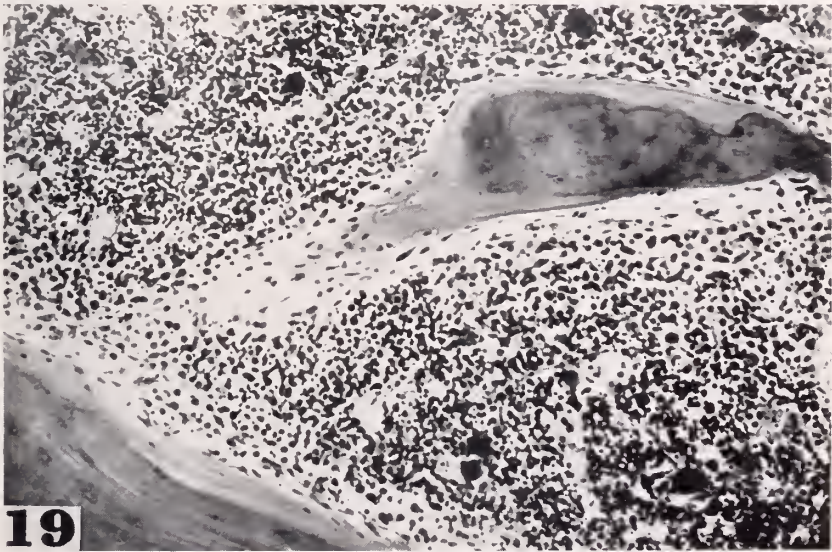
FIG. 17. Costochondral junction from 6 month old infant to show change of early rickets exemplified by defective deposition of inorganic materials in the cartilage matrix.

FIG. 18. Costochondral junction from 2 months old infant to show more extensive defects in the deposition of lime salts in the cartilage matrix. There has been acute cessation of deposition of inorganic elements. Note also the increase in width of mature cartilage cells.

mental animals rickets may be produced by a deficiency of one or more of three essential nutrients: calcium, phosphorus, vitamin D. In children the principle factor is an inadequate supply of vitamin D either in the diet or due to an accessory lack of sunlight, since ordinarily the absorption of ultra violet radiation by the skin leads to the formation of vitamin D in that tissue.

Rickets, like scurvy and the effects of inanition, manifests itself most severely in those bones growing at the most rapid rate. Hence its effects are seen most dramatically during the early years of childhood. The same is true in experimental animals. The first alteration is encountered in the provisional zone of calcification of the cartilage; here defects in the deposition of inorganic materials

appear. As a result of alterations in the humoral concentrations of calcium, phosphorus and, perhaps, other less well understood materials, there may be a spotty disturbance in deposition of inorganic materials (fig. 17), or in severe cases the entire width of hypertrophic cartilage may fail to show any deposit of organic elements (fig. 18). Cartilage cells continue to proliferate but fail to be invaded by blood vessels. The reason for this is not clear but may be related to changes in the metabolism of these cells due to alterations in the normal cycle of calcification. At any rate, in the acute, severe rickets (for one must take into consideration the duration as well as the severity of the bone disease) a microscopic section of the cartilage-shaft junction will show a broadened zone



19 FIG. 19. Trabeculae in shaft of a 7 month old child; note paler zone of osteoid about a portion of the calcified bone. Note irregular deposition of osteoid. (From *The Pathology of Nutritional Disease* by Richard H. Follis, Jr., M.D. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)

of hypertrophic cartilage cells, without any vestige of calcification or invasion by blood vessels. As time goes on and osteoblastic activity manifests itself, borders of osteoid begin to appear in irregular fashion about trabeculae and along the cortex of the shaft (fig. 19). With increasing duration of the derangement in serum calcium and phosphorus concentrations the changes at the cartilage-shaft junction become more pronounced. This region becomes increased in width and very irregular due to spotty invasion by blood vessels. Because of the lack of strength usually imparted by inorganic materials in this area, together with increasing amounts of weak osteoid in the shaft, deformity of the ribs or long bones readily occurs (fig. 20).

Roentgenographically the changes in such a bone (fig. 21) are characteristic. The irregular deposit of inorganic materials and rarefaction are readily explained on the basis of the events already referred to.

In the bones of children examined at autopsy, morphological changes characteristic of rickets are not at all uncommon. In a series reported some years

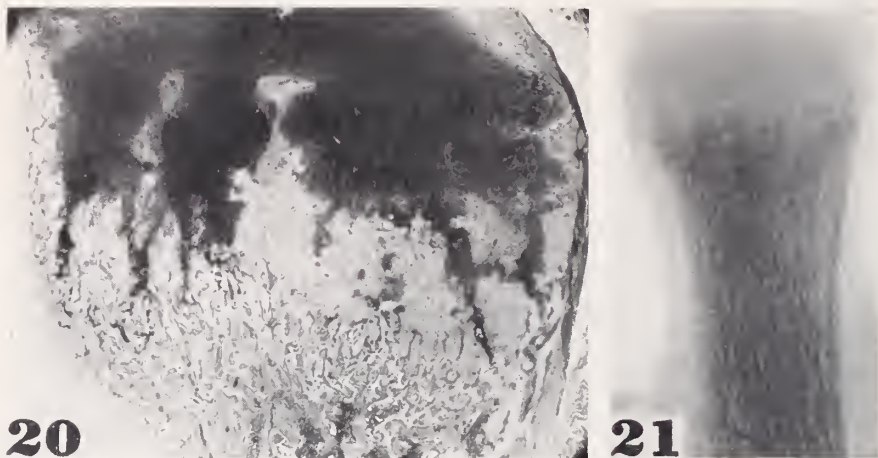


FIG. 20. Costochondral junction from a 7 months old child. Note irregularity in calcification and invasion of cartilage. (From *The Pathology of Nutritional Disease* by Richard H. Follis, Jr., M.D. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois).

FIG. 21. X-ray (positive print) of bone shown in figure 20. Note swelling of costochondral junction and irregular prolongations of calcification extending in to the cartilage.

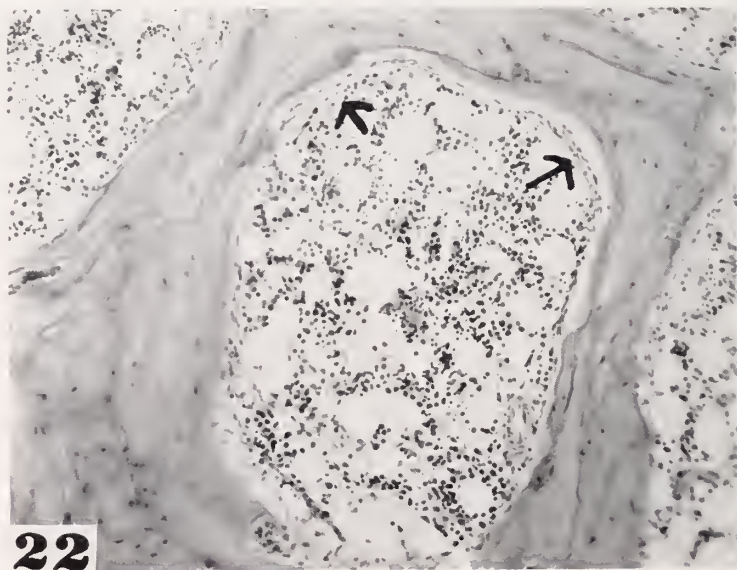


FIG. 22. Section of tibia from an adult dying of renal insufficiency as a result of chronic glomerular nephritis. Note bands of osteoid about trabeculae.

ago from the Johns Hopkins Hospital, rickets was found in 48.4 per cent of 487 children dying between the ages of three and nineteen months (9). A similar study of 230 children between two and fourteen years of age revealed morpholo-

gical evidence of rickets in 46.5 per cent (11). In both these surveys it must be emphasized that clinical evidence was not always present. However, as in the cases of scurvy already alluded to, such a method of evaluation of the prevalence of nutritional disease based entirely on morphological criteria furnishes the most precise data which one can obtain at this time.

Rickets in adults is called osteomalacia. We have not encountered osteomalacia at autopsy as a result of dietary deficiency. We (12) have observed numerous instances of excessive amounts of osteoid about the trabeculae of adults dying of chronic renal insufficiency (fig. 22). The mechanism here is undoubtedly related to the disturbance in calcium and phosphorus metabolism; the exact pathogenesis is not clear, however.

These changes in the bones which result from dietary deficiency have been described in a superficial manner. This has been partially due to a lack of time, but we must not let this excuse serve to cloak our ignorance of the fundamental mechanisms involved in the pathogenesis of the alterations we have described. It is hoped that with certain techniques now available we shall be able to answer certain more basic questions which I am sure have occurred to all of you.

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TORULA MENINGO-ENCEPHALITIS¹

JOSEPH H. GLOBUS, M.D., KENNETH M. GANG, M.D.

AND PHILIP S. BERGMAN, M.D.

[New York, N. Y.]

Torula invasion of the central nervous system is a relatively uncommon occurrence if its incidence is to be based on fully verified recorded cases. Only two such instances were encountered at The Mount Sinai Hospital in the past twenty-five years, and a survey of the literature discloses that a comparatively small number of cases of human torula infection have been reported² since this entity was first described some fifty years ago. Torula almost invariably invades the central nervous system, but the total number of cases of torulosis is somewhat higher than those with meningo-encephalitis.

Despite the fact that there are available several comprehensive reviews on this subject, giving excellent descriptions of the causative organism and the resultant histopathologic alterations, torulosis has received relatively little recognition among clinicians and has been correspondingly seldom invoked clinically in discussing differential diagnosis.

The following two cases are presented as good examples of this attitude, as well as of the difficulties encountered in arriving at a clinical diagnosis of torulosis.

CASE REPORTS

Case 1. History. (Adm. #464140, P.M. #11691) R. A., a girl, aged 20 years, a secretary by occupation, was apparently well until 17 days before entering The Mount Sinai Hospital (October 21, 1940), when she suddenly became aware of a throbbing, bilateral frontal headache, accompanied by considerable nausea. The headache increased in severity, and 3 days later she began to vomit after meals. In another 7 days she took to bed because of headache, vomiting and increasing generalized weakness. For the next 4 days the frontal headache was accompanied by a dull ache in back of her head and neck.

Examination. The patient was well developed and well nourished. The pharynx and tonsils were slightly injected. The lungs, heart and abdomen were normal. The blood pressure was 120 systolic and 70 diastolic; the pulse was 60 per minute.

The patient was somewhat drowsy, but well oriented and, in general, mentally clear. The optic discs showed slight blurring of the margins with some fullness of the veins. There was a bilateral external rectus weakness. The deep reflexes were depressed, while the abdominal reflexes were diminished. The plantar responses were equivocal.

Laboratory data. Urine, negative. Blood: hemoglobin, 13.9 Gm.; white blood cells, 13,600 with 81 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 1 per cent monocytes. Blood Wassermann reaction was negative; blood sugar, 95 mg. per cent; urea nitrogen, 9 mg. per cent.

X-ray examination: there was slight clouding of the left ethmoids; slight thickening of the inner table of the calvaria, and negative cervical spine and chest.

Electroencephalography revealed, at first, what was reported as a normal record, but

¹ From the Laboratories, Division of Neuropathology, The Mount Sinai Hospital, New York.

² A recent personal communication by Dr. Charles A. Carton indicated that he was able to find 225 such instances in the literature.

another encephalogram obtained at a later date showed "diffuse impairment of cortical function (increased pressure), but no cortical focus."

Course. An ophthalmological examination disclosed bilateral external rectus weakness, more marked on the left side, with corresponding homonymous diplopia; and bilateral early papilledema, somewhat more marked on the right. A lumbar puncture yielded clear, colorless fluid, containing 90 cells per cu. mm., chiefly lymphocytes. The initial pressure was 130 mm. of water; manometric readings indicated a delayed response. The Pandy test was one plus; the total protein was 51 mg. per cent. Colloidal gold and Wassermann tests were negative. The sugar was 60 mg. per cent; chlorides, 760 mg. per cent.

A nose and throat examination was reported to show a "mild chronic ethmoiditis;" an antral irrigation revealed no infection. A dental examiner found a small gingival lesion just below the lower left second bicuspid, which was thought to be an "abrasion."

The diagnosis of either *posterior fossa neoplasm* or *encephalitis* was under consideration.

A second lumbar puncture, performed one week after admission, revealed a partial block. The fluid, however, was similar in content to the first one. Following this procedure the patient's headaches increased in severity and were followed by vomiting. The papilledema, which at first seemed to be subsiding, began to increase; hemorrhages and a few exudates were observed in the right fundus. The bilateral abducens palsy increased and weakness of the internal recti appeared. There was a questionable right peripheral facial weakness. Slight bilateral ataxia and adiadochokinesis were elicited; plantar stimulation gave no response on the right side.

To rule out an intraventricular neoplasm or an obstructive hydrocephalus secondary to some inflammatory process, a bifrontal ventriculography was performed (November 18, 1940). This revealed a moderate internal hydrocephalus, more pronounced on the left side, with the posterior portion of the left lateral ventricle not visualized. The third ventricle was in the midline. The iter and the fourth ventricle did not fill. Subsequent lumbar punctures yielded cerebrospinal fluid under pressures of 480 and 500 mm. of water, containing as many as 380 cells, chiefly mononuclear. Later in the course of the disease the spinal fluid protein rose to 124 mg. per cent, and the sugar content decreased: in the second specimen it was 20 mg. per cent, and in the third there was only a trace. The question of tuberculous meningitis was then raised. The tryptophane test on the cerebrospinal fluid was reported to be negative. Guinea pigs were inoculated (the results, 8 weeks later, were reported as negative for tuberculosis). The patient's headache persisted, the papilledema continued to advance, reaching 5 diopters, and the patient became stuporous.

On November 25, 1940, a subtemporal decompression was performed. A biopsy specimen, consisting of the meninges and an adjacent piece of cortex, was reported as not showing any distinctive pathological alterations, but a specimen of cerebrospinal fluid examined at this time was reported (by Dr. Globus) as showing some significant elements: "A few cells are distributed in a homogeneously stained film. The cells vary in size from that corresponding to a small red blood cell to that of a large mononuclear leucocyte. Some of them provide the cell with a ring-like peripheral extension of nuclear material. Many of the cells show central vacuolization. An occasional cell shows cytoplasmic granules. Some of the larger cells have nuclei of the polymorphous variety. The impression is gained that the cells are hematogenous in derivation. Some are macrophages in character. Further identification is difficult and the suggestion is made that the cellular elements are indicative of parasitic invasion."

The next day another specimen of cerebrospinal fluid was obtained. It was studied and reported by Dr. Globus as follows: "A second specimen of cerebrospinal fluid was prepared in a much more satisfactory fashion. It shows a variety of cellular elements. Striking among these are small coccidioidal or yeast-like structures, characterized by a ring of denser protoplasmic material with a light, almost cystic, center (fig. 1). Some are partially collapsed. Occasionally one is seen in the process of budding. In addition, there are large macrophages with enclosures. Many flat, probably arachnoidal, cells are seen; some

of these also contain enclosures. I am inclined to diagnose this specimen as indicative of a yeast-like (*Torula*) invasion of the nervous system, with meningeal reaction."

Repeated lumbar punctures continued to yield turbid fluid under very high pressure (500 mm. of water) and contained as many as 400-500 mononuclear cells. A culture of the

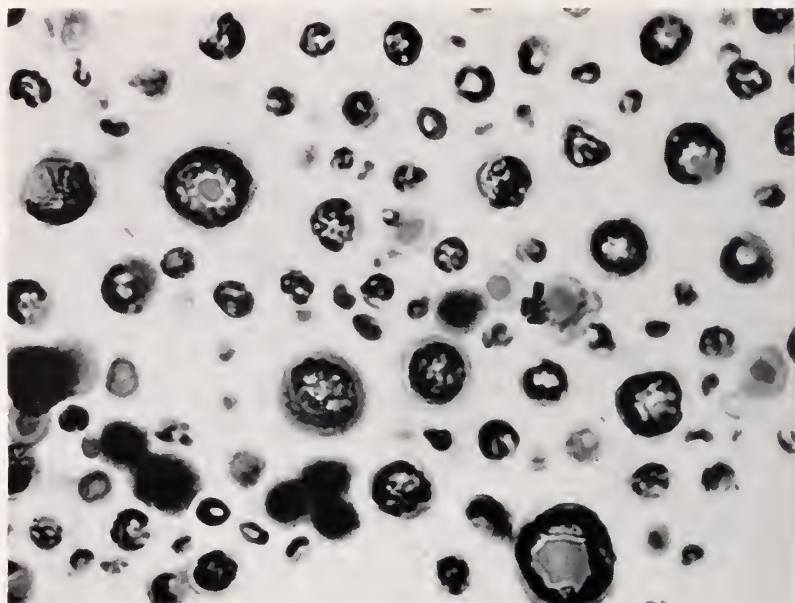


FIG. 1. (*Case 1*) The torula organism in centrifuged cerebrospinal fluid, embedded in paraffin and sectioned. Hematoxylin and eosin stain, $\times 1080$.



FIG. 2. (*Case 1*) Torula organisms, showing the body of the cell, the refractile membrane, the intracellular granules, the capsule and budding. India ink preparation, $\times 1000$.

cerebrospinal fluid on routine media yielded a growth identified as *Cryptococcus hominis* (*Torula*). When stained with India ink it demonstrated a wide, clear capsule, two or three times the thickness of the cell itself (fig. 2). There were granules present in the cell body. Some of the yeasts were budding.

A culture injected intravenously into mice resulted in the finding of characteristic lesions

in the central nervous system. The Bacteriology Department confirmed the diagnosis of torula meningitis. Sulfanilamide was administered but the patient's condition declined rapidly and she died on December 5, 1940, two months and two days after the onset of the illness.

Necropsy findings. Brain. In the region of the right temple, the scalp bulged and there was a palpable, round defect in the skull, about 3 cm. in diameter, which was the site of a recent subtemporal decompression. When the scalp was reflected, the part overlying the bony defect was seen to be slightly thickened. It was adherent to the underlying muscle by means of a poorly organized mass of fibrin and connective tissue. The dura was normal except in the vicinity of the herniation in the right temporal region, where it was covered by a small amount of dark clotted blood and a thick, grayish-yellow, viscid material. The dural sinuses were patent throughout.

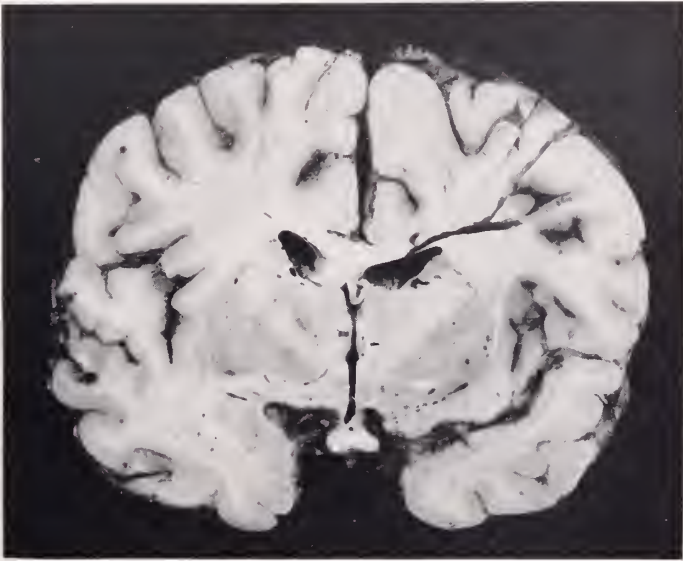


FIG. 3. (Case 1) Coronal section of the brain, showing many punctate markings indicating the site of minute gelatinous cysts.

The brain appeared normal in outline but was markedly edematous, with flattened gyri and shallow sulci. There were no localized areas of altered consistency, the whole brain being diffusely involved in the edema.

The leptomeninges over the entire brain appeared thickened and cloudy; this was especially true over the base of the brain, in the region of the interpeduncular and pontine cisterns, where the meninges were markedly thickened. The leptomeninges were adherent to the dura at the site of the right subtemporal decompression and on the basal surface of the frontal and temporal poles. An increased amount of cerebrospinal fluid in the subarachnoid space had the appearance of a thick, viscid, gray, slimy exudate which was present over the entire surface of the brain and in greatest quantity at the base of the brain.

On sectioning the brain, the ventricular system was found to be only moderately dilated; there was slight asymmetry, with the ventricles on the decompressed side being somewhat deformed. Throughout the substance of the brain, there were visible minute, cyst-like cavities (fig. 3). They were most readily recognized in the basal ganglia and were also seen in the cortex and the subcortex. Their distribution was quite irregular. The sulci were filled with a gelatinous material like that noted in the subarachnoid space on the surface of the brain.

Microscopic observations. Sections of the cerebrum, medulla and a cranial nerve were stained with hematoxylin and eosin. A cellular exudate was present in the subarachnoid space (fig. 4). It was predominantly mononuclear but contained many lymphocytes, forming a cuff around blood vessels in the subarachnoid space and also around vessels extending into the brain substance (fig. 5a). There were many giant cells containing several oval or round nuclei, centrally placed and with inclusions of small, clear, circular yeast cells surrounded by halo-like areas. Many yeast cells were in the process of budding and were free in the cerebrospinal fluid. The brain substance revealed many cystic areas, varying in size and in many cases consisting of a coalescence of small cysts (fig. 5b). These areas were clear and occupied by many circular yeasts as well as mononuclear cells and compound granular corpuscles. The remains of a capillary or small blood vessel could usually be demonstrated in the center of these areas.

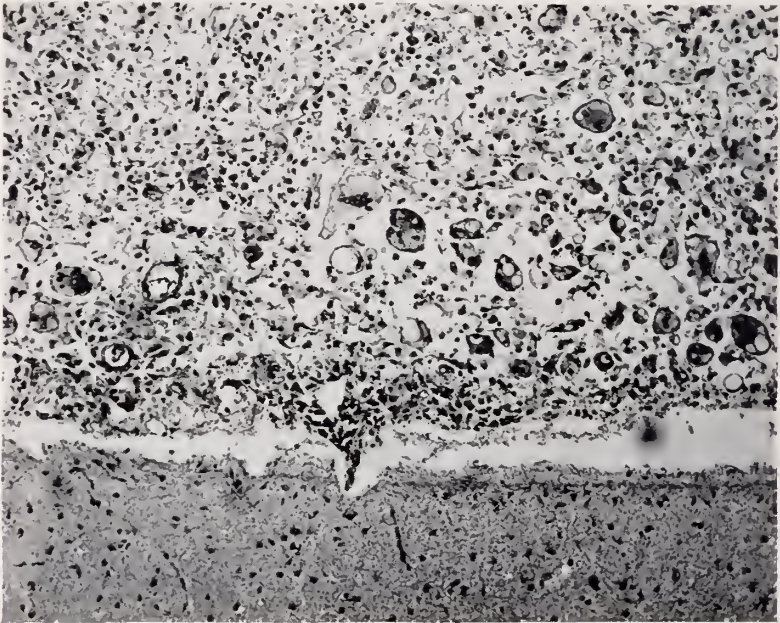


FIG. 4. (Case 1) Section of cerebral cortex and overlying meninges, showing numerous organisms intermixed with a number of macrophages in the subarachnoid space. Hematoxylin and eosin stain, $\times 120$.

Comment. The clinical features in this case are characterized by an abrupt onset of symptoms pointing to some intracranial disease. As the disease process advanced and the clinical manifestations assumed the character of a meningo-encephalitis, its tuberculous etiology was strongly suspected and somewhat supported by cerebrospinal fluid findings such as pleocytosis and lowering of the sugar content. However, an expanding lesion with secondary inflammatory reaction was, justifiably, not fully excluded. It was only an examination of the cerebrospinal fluid with an eye for unusual cellular components that uncovered the true etiologic factor. Thus, it argues for the need of thorough search by the experienced for the causative organism among the cellular elements in the cerebrospinal fluid so that the correct diagnosis may be made.

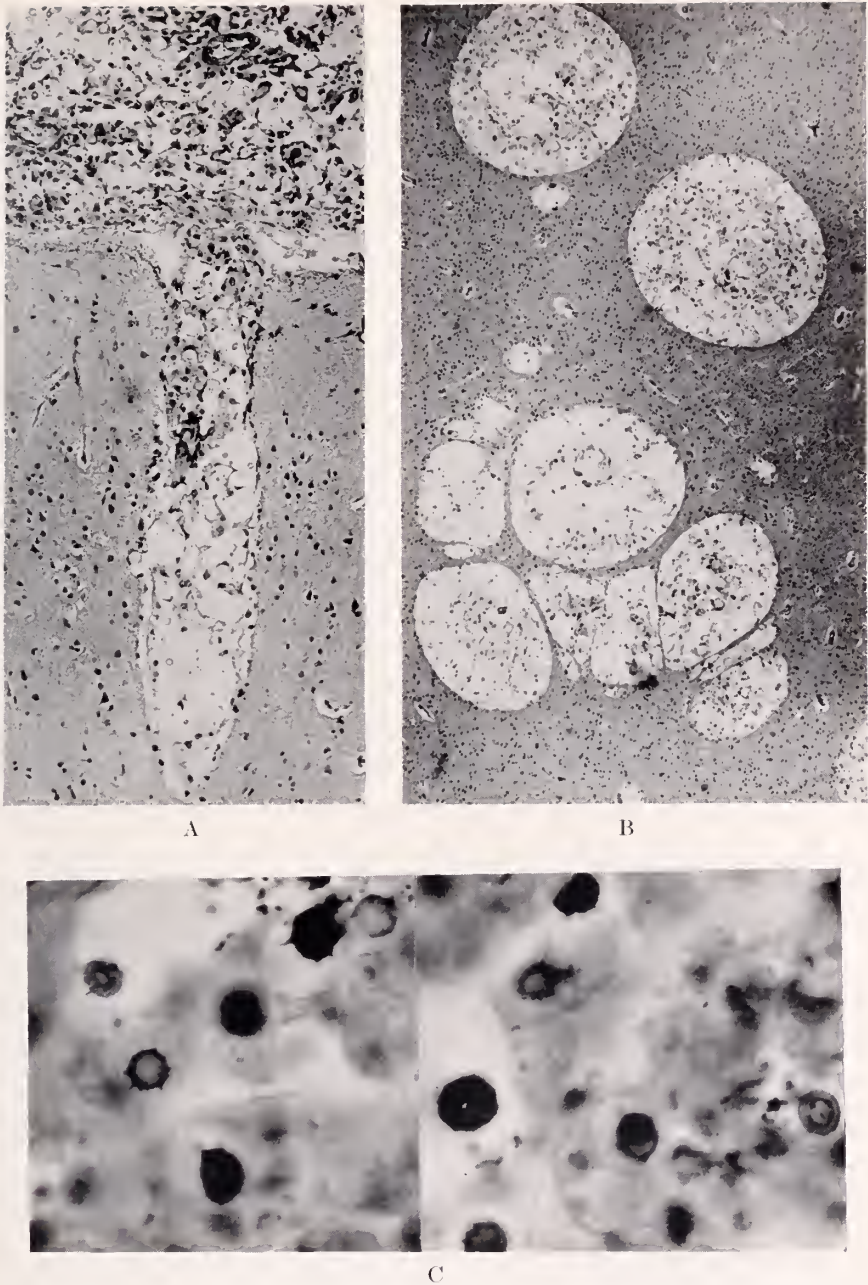


FIG. 5. (Case 1) A. Section of cerebral cortex and adjacent meninges, showing the extension of the exudate, containing the organism, into the perivascular space of the penetrating blood vessel. B. Section of cerebral cortex, showing several cysts, which, as can be seen, are nothing more than the perivascular spaces distended by the exudate. Hematoxylin and eosin stain, $\times 105$. C. Torula organisms in a perivascular space of the brain, exhibiting radial spikes and distinct capsules (Toluidine blue stain; $\times 500$).

Case 2. History. (Adm. #485084, P.M. #12087) This patient, B. K., an attorney by occupation, entered The Mount Sinai Hospital for the first time on November 26, 1940, at the age of 40 years. For many years he had been subject to recurrent headaches which were relieved by ordinary medication. Two months prior to his admission he was seized with severe headaches, accompanied by nausea and vomiting. Shortly thereafter he developed vertigo and weakness of the legs, causing marked unsteadiness of gait. He became irritable, depressed, exhibited memory impairment and had difficulty in concentrating. He continued, nevertheless, to work until the day of admission.

Examination. The patient walked on a wide base, with a slightly unsteady gait and a tendency to veer to the right. There was a slight left internal strabismus, with diplopia on left lateral gaze and on convergence. The discs showed some choking, more marked on the left side. An equivocal Babinski sign was elicited on the right side. His speech was slow and deliberate.

Laboratory data. A lumbar puncture yielded clear cerebrospinal fluid, which was colorless and under an initial pressure of 260 mm. of water, with the final reading, after removal of 3 cc. of fluid, at 210 mm. of water; the dynamics were normal. The cerebrospinal fluid contained 250 cells per cu. mm., 50 per cent of which were polymorphonuclear leucocytes, and a total protein of 320 mg. per cent. The Wassermann reaction was negative. Pandy was negative. The colloidal gold curve was: 3332211000.

Ventriculography revealed marked symmetrical dilatation of the lateral ventricles with similarly marked dilatation of the third ventricle; there was no displacement. The aqueduct was not visualized. An endolumbar encephalography showed air blocked at the level of the foramen magnum.

An electroencephalogram was interpreted as showing no evidence of an expanding lesion in the hemispheres. Diffuse delta activity indicated increased intracranial pressure. This slow activity dropped out temporarily, indicating probable fluctuations in pressure. The report (by Dr. Hans Strauss) read further, "a third ventricle tumor does not seem probable. A lesion in the posterior fossa seems more probable with the decrease of alpha activity in the left occipital region suggesting a possible left-sided cerebellar tumor. The focalizing signs are, however, very meager."

Course. On the basis of the original neurologic status, a *neoplasm, probably in the left frontal lobe*, was considered, but when the pneumo- and electroencephalography findings became available the diagnosis of a *posterior fossa lesion* was made, either neoplastic or inflammatory in nature. An exploratory suboccipital craniotomy was then carried out and the arachnoid covering the cisterna magna was found to be thickened and opaque. The cerebellar tonsils were found adherent to the floor of the fourth ventricle and to the upper part of the spinal cord. The tonsils were separated, but it was impossible to free them enough to look into the fourth ventricle. A needle was then introduced into the fourth ventricle, and a large amount of clear, colorless cerebrospinal fluid was obtained. A few yellow patches were observed on the posterior and lateral surfaces of the upper portion of the spinal cord; the roots of the spinal accessory nerves were covered with exudate. Two fragments of leptomeninges were removed. The histopathologic study of these was reported by Dr. Globus as showing infiltration of the arachnoid with small, dark-staining cells, which had the appearance of small lymphocytes; some of these cells were fusiform in shape. An occasional large, multinucleated cell was seen. No conclusion could be reached as to whether the lesion was sarcomatous or inflammatory in nature. It was assumed by the surgeon that the meningitic process closed the foramina of Magendie and Luschka, resulting in internal hydrocephalus.

Following the operation the papilledema receded and the cerebrospinal fluid pressure dropped to 170 mm. of water. X-ray therapy was administered and continued for some time following the patient's discharge from the hospital, which took place on December 29, 1940.

Interval history. While at home, the patient continued to improve in the course of the next 9 months. At the end of this time, recurrence of severe headache and projectile vomiting terminated his progress to recovery. He became alternately drowsy, depressed,

and irritable and displayed impairment of memory. A tendency to fall backward made it exceedingly difficult for him to walk. He reentered the hospital on January 29, 1942.

Second admission. The patient was somewhat drowsy and otherwise showed marked psychomotor retardation. There was slight blurring of the disc margins on the left; diminished visual acuity, more marked on the left; and restricted conjugate deviation of the eyes to the left. There was moderate nystagmus on lateral gaze to either side and on upward gaze. The pupils were equal but reacted sluggishly in accommodation. There was a left central facial weakness. Motor power was generally poorly sustained, with marked inward and upward drift of the right arm. The deep reflexes were equal and active. The plantar response was diminished bilaterally. The Romberg sign was marked, with the patient falling to the left and backwards. A slight dysdiadochokinesis, a definite rebound phenomenon, and moderate ataxia on finger-to-nose and heel-to-knee tests were present. Position sense was diminished in the fingers and toes. The blood pressure was 112 systolic and 80 diastolic. The blood count, serologic and chemical determinations were within normal limits.

Course. Sarcomatosis of the meninges and expanding posterior fossa lesion were again considered as diagnostic possibilities. A lumbar puncture yielded cerebrospinal fluid under an initial pressure of 160 mm. of water, containing 51 cells (85 per cent lymphocytes and 15 per cent polymorphonuclear leucocytes).

On February 3, a ventricular puncture was performed; 80 cc. of clear cerebrospinal fluid were removed and replaced by 85 cc. of air. The fluid was under a pressure of 370 mm. of water. It contained 5 red blood cells and 5 lymphocytes per cu. mm. The Pandy reaction was 2 plus. Fifty cc. of ventricular fluid were centrifuged; the sediment was spread on a slide and stained with hematoxylin and eosin. There was found a large number of scattered mononuclear elements having the appearance of lymphocytes, but their true nature could not be determined.

Bacteriological study of cerebrospinal fluid revealed no growth, aerobically or anaerobically.

The ventriculogram showed a huge, symmetrical dilatation of all the ventricles, without shift. The cerebrospinal fluid pressure in the right lateral ventricle measured 360 mm. of water with the patient in a semi-recumbent position.

The question of subjecting the patient to a second exploration was considered, but in view of the histologic report of a diffuse meningitic process, and since the previous operative site did not appear to be tense, operation was felt not to be indicated until such time as relief of the hydrocephalus should become imperative. An electroencephalogram was reported to be more abnormal than the previous one, but still not characteristic of any specific lesion.

On the morning following the ventriculography the patient suddenly became cyanotic and unresponsive. Examination disclosed blurred discs, a fixed, dilated right pupil, absent tendon reflexes in both upper extremities, and hyperactive tendon reflexes in both lower extremities with bilateral ankle clonus. The patient's respirations became irregular, and he died shortly thereafter, 6 days after his second admission to the hospital.

Brain. Gross. There was fairly marked injection of the surface vessels of the brain. The gyri were flat and the sulci narrow. On the surface of each superior parietal lobule, at the site of the ventricular punctures, there was a brown discoloration measuring 0.5 cm. in diameter. The dorsal surface of the medulla was somewhat adherent to the cerebellar tonsils. The left cerebellar tonsil was soft, and on its posterior surface there was a dark area of discoloration about 1.5 cm. in diameter. The structure between the flocculus and the cerebellopontine angle on the left side was softer than normal. The arteries at the base of the brain were normal except for slight thickening of the left vertebral artery. The dural sinuses were patent.

On sectioning of the brain, there was noted a marked, bilaterally symmetrical hydrocephalus affecting all the ventricular compartments, including the aqueduct of Sylvius. The fourth ventricle was widely dilated in its anterior portion, and the tonsils were seen

projecting into it. The posterior end of the ventricle seemed to be completely occluded by adhesions, so there was no communication between the fourth ventricle and the cisterna magna (fig. 6). The medulla oblongata seemed to be somewhat flattened dorsoventrally. The central canal in the closed portion of the medulla appeared to be occluded. The ependymal lining of the fourth ventricle was somewhat thickened, and the ventricular walls were covered with pinkish, fluid material throughout. Air mixed with cerebrospinal fluid was still present in the ventricular system.

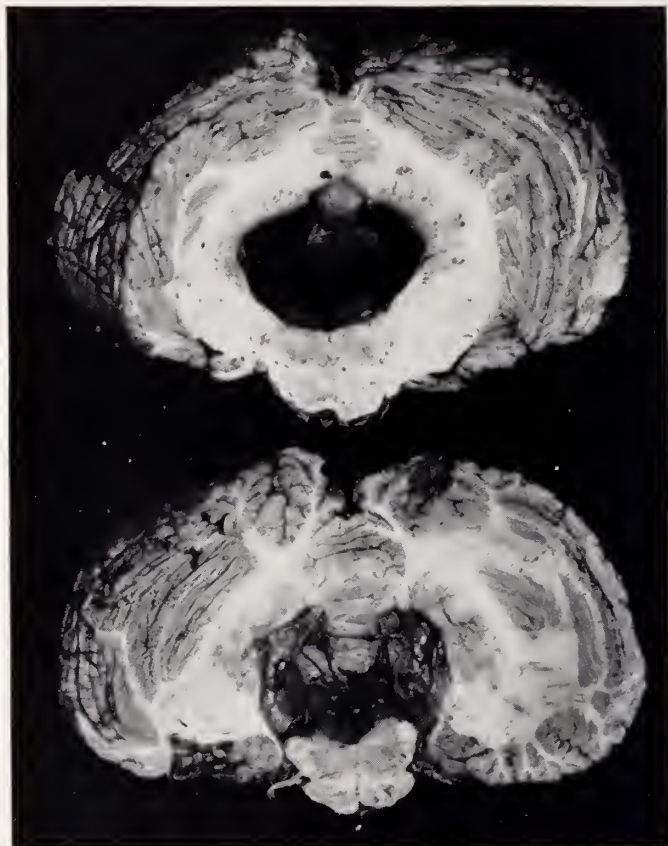


FIG. 6. (Case 2) Coronal sections of the cerebellum, showing the marked enlargement of the 4th ventricle and (in the lower section) the mucinous exudate sealing the posterior end of the 4th ventricle.

Microscopic observations. Sections of the cerebellum revealed the more significant alterations at the periphery. Here the most striking change was in the leptomeninges (fig. 7a). They were thickened and displayed a fair increase in the collagenous material, appearing in places as short, fine threads or narrow, hyalinized bands. Within the meshes of this tissue, there was a moderate number of small round cells, some of which formed incomplete rings about blood vessels (fig. 7b); a few red blood cells; some polymorphonuclear leucocytes and a few macrophages. An occasional multinucleated giant cell was encountered in the denser areas of infiltration (fig. 8). The nuclei in such a cell were arranged at the periphery. There were also found a few collections of cells with overlapping nuclei, suggesting giant cell formation.

Scattered in the affected areas of the leptomeninges there were noted peculiar, homogeneous, spherical bodies (fig. 9). They were all of a size larger than red blood corpuscles and some were several times the size of a polymorphonuclear leucocyte. The spherical bodies were pink or pale blue in hematoxylin and eosin preparations. They had a smooth, well

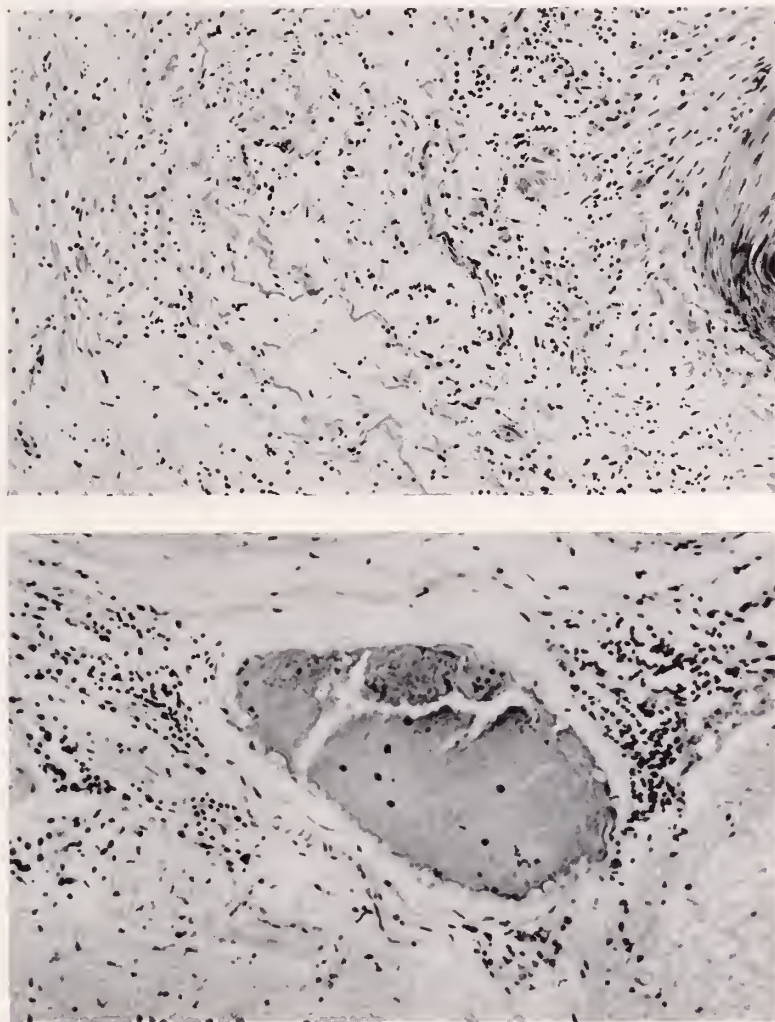


FIG. 7. (Case 2) A. Section of the meninges covering the roof of the 4th ventricle, showing a moderate, subacute, productive inflammatory process. Hematoxylin and eosin stain, $\times 105$. B. Section of meninges in proximity to the roof of the 4th ventricle, showing a more pronounced inflammatory reaction, typified by lymphocytic perivascular infiltration. Hematoxylin and eosin stain, $\times 120$.

defined, capsule-like margin. In some areas they were found in clumps of three or four, overlapping one another.

Because of a recent experience with a case of torula meningitis, and the resemblance of these spherical bodies to torulas, special stains were applied.

With the Gram stain, the spherical bodies acquired a deep purple color and displayed a double contour. A Ziehl-Neelsen stain failed to disclose tubercle bacilli. Other stains

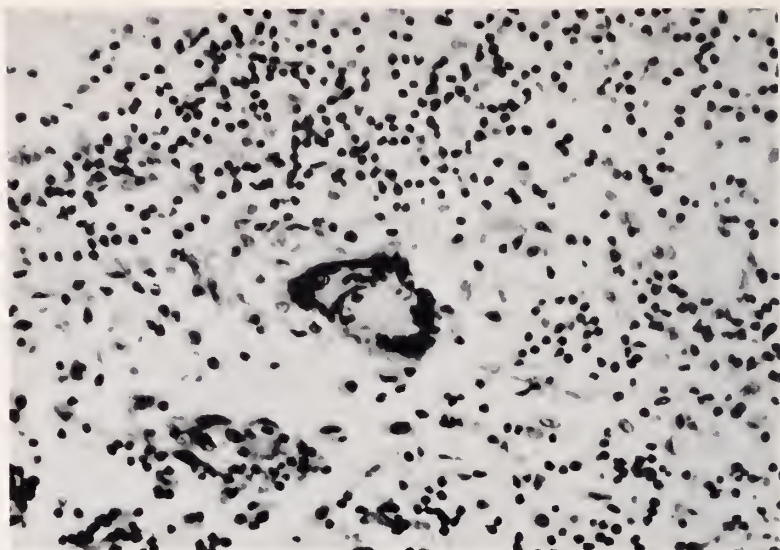


FIG. 8. (*Case 2*) Section of meninges in the proximity of the roof of the 4th ventricle, showing giant cells in an area of focal lymphocytic infiltration. Hematoxylin and eosin stain, $\times 325$.

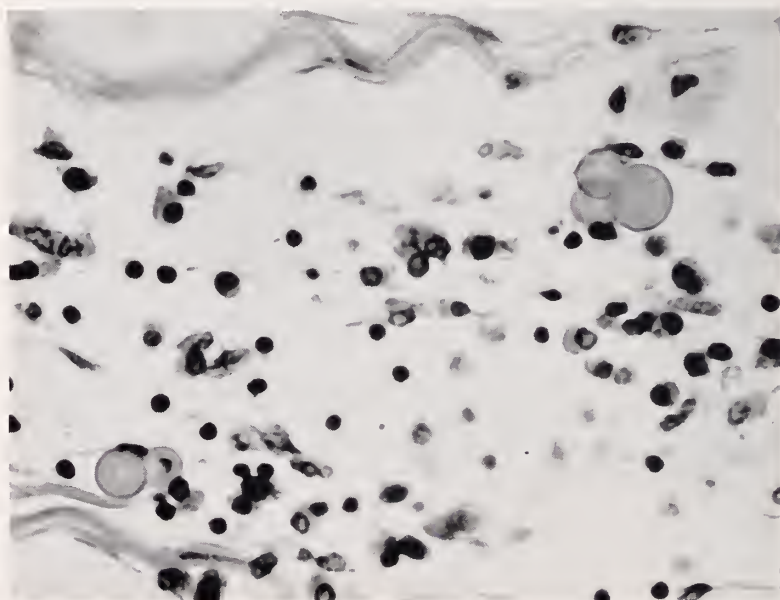


FIG. 9. (*Case 2*) Section of meninges in the proximity of the roof of the 4th ventricle, showing the characteristic appearance of the torula organisms. Hematoxylin and eosin stain, $\times 630$.

were employed, but the most satisfactory results were obtained with the one recently suggested by Kernohan (1). By this method it was possible to detect them in larger numbers. The stain also revealed them in the cerebellar tissue (fig. 10). There, although they were

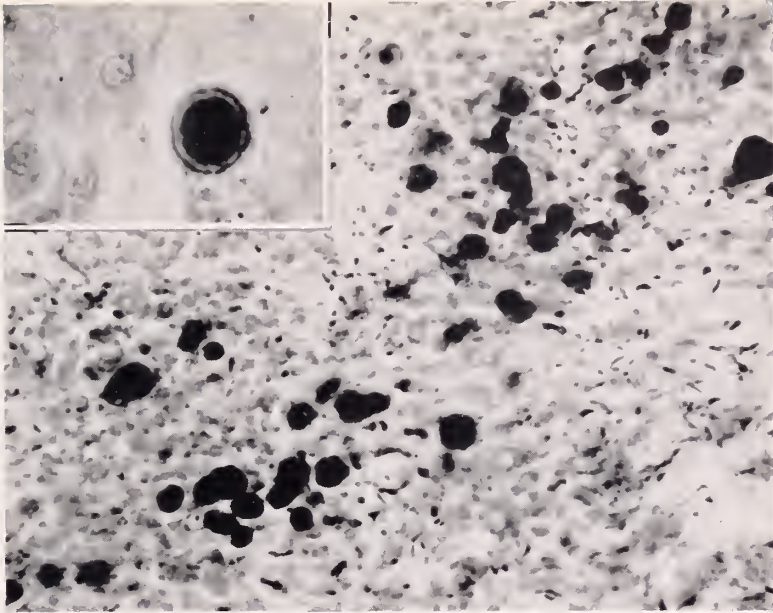


FIG. 10. (*Case 2*) Section of the meninges and adjacent cerebellar cortex, showing the torula organisms as they appear under high magnification. Kernohan's stain, $\times 550$; (Inset, $\times 1000$.)

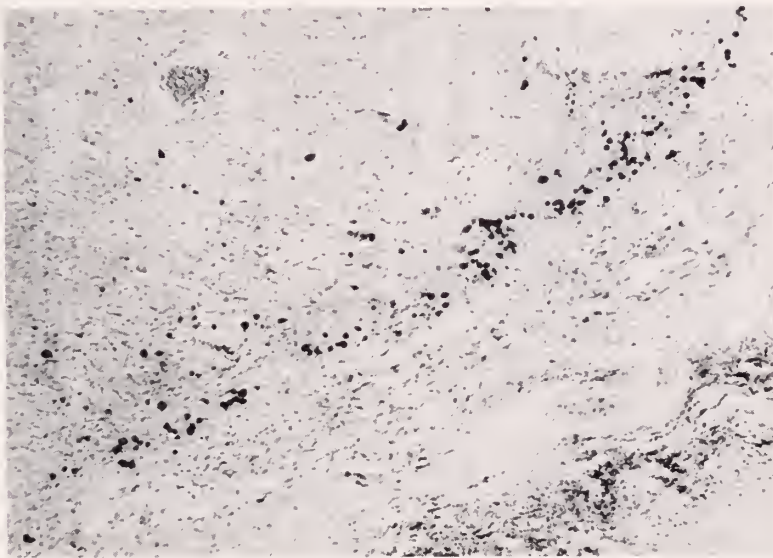


FIG. 11. (*Case 2*) The torula organisms arrayed along the surface of the cerebellar cortex and overlying meninges. Kernohan's stain, $\times 105$.

found only in small numbers in the deeper tissue, they were numerous at the periphery (fig. 11).

Sections of the cerebrum revealed only slight thickening and increased cellularity of the

pia-arachnoid. The nerve cells were fairly well preserved, the blood vessels were free of significant changes and no torulas were seen.

Sections of the cerebellum, aside from the presence of the torula bodies, disclosed no significant alterations. Some of the Purkinje cells showed pyknotic, eccentric nuclei in addition to chromatolysis and vacuolization of the cytoplasm.

Comment. The clinical manifestations and course in this case did not differ substantially from those in Case 1. One would be justified in raising the question, why, with the experience gained in Case 1, was the causative organism not recognized in the cerebrospinal fluid or biopsied tissue of Case 2? There is really no satisfactory answer, except to say that greater experience and greater tenacity in search for the organism are, indeed, essential, though not always insuring success, as demonstrated by this case. Here, even in the postmortem material, the organism was found only after a thorough search and in relatively small numbers, and a reexamination of the antemortem biopsied material failed to disclose torulas. Thus, it becomes clearer why in some instances, as in this one, the causative agent is so elusive.

DISCUSSION

It was already pointed out that in almost all recorded cases the diagnosis presented a most difficult problem. The reason for this is to be found in the fact that the symptoms and signs in this disease do not form a pathognomonic constellation. The two cases herein reported are no exceptions to this. Neither exhibited clinical features which could be regarded as diagnostic of the underlying disease process.

In Case 1, the clinical course and the early objective findings were consistent with the diagnosis of posterior fossa tumor. It was the later course, with the appearance of increasing pleocytosis in the cerebrospinal fluid, that aroused the suspicion of a chronic productive meningitis, such as tuberculous meningitis. The rapid progression of symptoms of increased intracranial pressure demanded surgical intervention, but even when biopsied material was made available the diagnosis of torulosis could not be made.

In Case 2, the clinical picture again led to an initial diagnosis of posterior fossa tumor, and here again biopsy material failed to aid in a final and correct diagnosis.

A survey of the literature discloses that the disease in its early phases is most likely to arouse the suspicion of tuberculous meningitis, because of the dominant meningeal signs and symptoms, the pleocytosis and the low sugar content in the cerebrospinal fluid, and the subacute or chronic clinical course. Other forms of chronic meningitis (syphilitic, lymphocytic choriomeningitis) and encephalitis are other diagnoses often erroneously made in connection with torula meningo-encephalitis (2).

Not infrequently, because of the nature of the pathologic alterations in this disease, causing an interruption in the flow and in reabsorption of the cerebrospinal fluid and provoking signs of increased intracranial tension, the presence of an expanding cerebral lesion is strongly suspected. Because of that, and in spite of prominent manifestations of meningeal irritation and features of an inflamma-

tory reaction, intracranial exploration is often carried out. No neoplasm, of course, is found and only rarely are there encountered torular granulomas, single or multiple, which are mistaken for neoplastic lesions. Biopsied tissue reveals inflammatory changes of a somewhat unusual type. It follows that a correct diagnosis can be reached only on the recovery and full recognition of the causative agent. It is thought desirable, therefore, to present at this point a summary of the biologic characteristics of the organism causing torulosis.

The Torula and methods for its detection. The organism is a yeast, named correctly according to the accepted rules of nomenclature, *Cryptococcus neoformans* (3). The name *Torula histolytica*, erroneously given to this organism in 1916 by Stoddard and Cutler (4) as a result of their otherwise excellent study, is so commonly used that it cannot be abandoned without causing confusion. The qualifying term, *histolytica*, could well be dropped since it implies properties the organism does not possess. The details of the misunderstandings that led to the general adoption of this name without biologic justification, given in Benham's review (5), make an interesting study in nomenclature. The organism is encountered in the literature under many other names, among them *Cryptococcus hominis*, *Debaromyces neoformans*, *Torulopsis spp.*, and *Saccharomyces spp.* European blastomycosis is a fairly common synonym for the disease; there is little or no justification for using it.

The organism has a varied appearance, depending on whether it is examined in culture, in body fluids, or in pathologic lesions. Generally, it is a round to oval body, 1-15 μ in diameter, surrounded by a transparent capsule some 3 to 5 times the size of the cell itself. It usually has a sharply defined, double wall. (The cells pictured in Figure 2 are typical.) In some preparations it exhibits irregular spikes radiating from the body of the cell. Hassin (6) believes these spikes are intrinsic features of the organism while others (7) regard them as artefacts. Though uncertain as to the meaning of the spikes or to the constancy with which they occur, we have succeeded in demonstrating them regularly wherever these organisms were found, using a method similar to that employed by Hassin³. It may be significant that the same stain when applied to paraffin- or celloidin-embedded material failed to reveal these spikes. Budding forms are common, but no spores or hyphae are demonstrable (in old cultures, kept for several weeks, occasional feeble, branched hyphae may be encountered); mycelial threads are not formed.

The organisms stain with the common dyes without uniformity. With hematoxylin and eosin, they take on a color which varies from bright blue to pink; occasionally they display no color at all. Generally, the cell body is Gram-positive while the capsule is Gram-negative; this, also, is not constant. A fairly dependable reaction is obtained with Wright's (Leishman's) or Giemsa stain,

³ Our method consists of staining sections, cut with the freezing microtome, for 5 minutes in 0.25 per cent aqueous solution of toluidine blue and differentiating them in aniline oil-alcohol. The organisms take a bright violet coloration which clearly distinguishes them from the surrounding brain tissue, blood vessels and exudate, all of which stain uniformly light blue.

differentiating the organism clearly from leukocytes (7, 8). Kernohan (1) has devised a special staining method for a reliable identification of *Torula*, *Coccidioides* and *Blastomyces*. In Hassin's experience (6), toluidine blue and thionin are satisfactory as stains for these yeasts, particularly to demonstrate the radiating spikes. Blair (9) found that these dyes did not always give reliable results.

The organism usually grows readily on routine laboratory media, but a faster and more luxuriant growth is obtained on blood agar, Sabouraud's agar or Loeffler's medium. It is quite resistant to drying; Cox and Tolhurst (7) kept a specimen of cerebrospinal fluid dried at room temperature for 10 months; at the end of that time a culture yielded an excellent growth. The yeast is killed at 60°C. within 5 minutes (7), and at 105° and 107°F. (40.5° and 41.7°C.) in 6 to 7 days (10).

The clinical diagnosis of torula meningo-encephalitis is admittedly difficult, if not to say impossible, without the identification of the causative organism. It is a challenge that must be met in every instance of a chronic meningitic process in which tuberculosis and syphilis are excluded; in instances of increased intracranial pressure, with or without localizing signs, associated with pleocytosis and xanthochromia in the cerebrospinal fluid; and in any obscure disease of the central nervous system in which there is found a pleocytosis of the cerebrospinal fluid. In such situations the identification of the causative organism becomes imperative. The following laboratory investigations in this direction are found most useful:

1. The cerebrospinal fluid, unstained or treated with 0.2 per cent methyl violet in 1 per cent acetic acid, is best examined in a blood counting chamber or in a hanging-drop slide. With reduced illumination, the organisms may be readily identified as round bodies about the size of white blood cells, surrounded by a clear "halo" (the capsule) about 3 times as large as the cell. Buds are occasionally seen, and the interior of the cell may contain several small, globular bodies (fig. 2) (these can be stained with Sudan III and are presumably lipid). In the stained fluid, the cells acquire a light, homogeneous blue color, contrasting with the irregular outline and deep blue color of leukocyte nuclei; the capsule does not stain.

2. The cerebrospinal fluid, evaporated almost to dryness and emulsified with a drop of India ink on a slide, is pressed down hard with a cover glass to form a thin film. The unstained parasites, if present, contrast sharply with the surrounding dark field appearing as round bodies with a double wall and an enveloping wide, clear halo (11). This method may also be used in identifying the organism in culture (Figure 2 was taken from culture material).

3. A smear prepared from the sediment of centrifuged cerebrospinal fluid,⁴ stained with Wright's or Giemsa stain, will reveal the yeasts, if present, and because they stain homogeneously will be readily distinguished from white blood cells. Gram's method is less satisfactory, but may be improved by drying the smear on a slide, covering it for 2 minutes with 40 per cent formalin, washing thoroughly with water, then staining (12).

⁴ It was pointed out by Blair (9) that the organisms may be destroyed by centrifuging.

4. Culture. A quantity of cerebrospinal fluid is best planted on Sabouraud's, blood agar, and Loeffler's medium. Within 4 or 5 days—occasionally within 24 hours (7), but sometimes not before 2 weeks (2, 13)—round, raised, sharply-defined, gray, non-hemolytic colonies will be seen. Unstained saline suspensions of these colonies will show the characteristic organisms, but the capsules are not so prominent as in "natural" material; they will be readily discerned, however, in India ink preparations. Mager and Aschner (14) showed that cultures of *Torula* produce starch, which may be identified by flooding the plate with Lugol's solution. Other yeasts which may be confused with *Torula* in cultures are *Oidium* (arthrospores are formed) and *Coccidioides* (endospores are formed), while no spores are formed by *Torula*. However, the appearance alone is characteristic: *a yeast with a wide capsule around it is nothing else but Torula*.

5. Animal inoculation is another important step. Fresh material or cultural growth is injected intraperitoneally in mice. The disease proves fatal in 3 or more weeks and autopsy will disclose the characteristic lesions in most of the organs, including the central nervous system. Animals should not be considered negative until at least 6 months have elapsed (2).

6. Histopathologic studies. Biopsied material stained by almost any method shows the organism and a characteristic pathologic reaction. Conant and co-workers (15) suggest, for rapid diagnosis, the staining of frozen sections with undiluted Giemsa stain. Post-mortem material, formalin-fixed and paraffin embedded, is examined with the routine stains. The Kernohan modification of the Best-Bodian stain has been most satisfactory in our experience. This method, as well as toluidine blue or thionin, should always be used if the hematoxylin and eosin stain is inconclusive. (In all methods employing paraffin embedding, the capsules are poorly demonstrated, as shown in Figure 1.)

7. Other diagnostic methods:

- a. Serological reactions have not proven to be of any value (7, 15).
- b. Skin tests seem to have provided diagnostic information in some cases (3), but generally were found unreliable (7).
- c. Blood or urine cultures have, in a few cases, revealed the organism, which has also been found in stained sputum (12, 16). These procedures proved negative in most patients.

The cerebrospinal fluid in torulosis. While the fluid (aside from containing the specific organism generally reveals no characteristic features, there are fairly constant findings which deserve comment. The fluid is often xanthochromic and may be turbid. The pressure is almost always increased, sometimes to very high levels. A cell count (generally 200–800 per cu. mm.) usually reveals a high proportion of lymphocytes, although there may be up to 50 per cent polymorphonuclear leukocytes. It has been suggested that many of the presumed mononuclear cells are actually torulas; *unless the possibility of torula infection is kept in mind and suitable precautions taken the organisms can easily be mistaken for lymphocytes*. Sugar in the cerebrospinal fluid is usually lower than normal and may be sharply reduced or altogether absent. Chloride determinations often show a decreased content, sometimes going lower than in tuberculous meningitis

(17). The protein is almost always elevated, both the albumin and globulin fractions participating; because of this alteration the colloidal gold curve may give reactions indistinguishable from those seen in parenchymatous neurosyphilis. The Wassermann reaction, unless there is coexisting syphilis, is always negative.

Histopathologic alterations (summarized). Torulosis exhibits fairly characteristic lesions in the central nervous system. In exceptional instances there are granulomatous lesions which are indistinguishable from tubercles. Usually there is a diffuse meningitis, from which the exudate typically extends into the perivascular spaces. The latter become distended, giving the appearance of multiple, grayish, gelatinous cysts in the brain substance. The exudate elsewhere is also characteristically gray and gelatinous. This mucoid consistency of the lesions has led to the commonly encountered description, "myxomatous." The "jelly" is probably a coalescence of the capsular material of the organism (7). As a rule, there is little or no reaction in the brain tissue surrounding the distended perivascular spaces—which may sometimes reach great size—and the appearance of sharply demarcated, cystic areas filled with jelly-like material is typical of this disease. This "soapsuds" appearance is also evident microscopically (fig. 5b). Microscopic studies, even with lower magnification, will bring into view the organism in large numbers, dispersed in mononuclear exudate. The absence of glial reaction is striking, especially when a large lesion is present. Giant cells are often encountered in the meningeal exudate, but usually not in the brain itself, except in the rare tubercle-like lesions, where their cytoplasm may contain one or more torulas.

Differential diagnosis. Torulosis of the central nervous system simulates tuberculous meningo-encephalitis so closely that without the isolation of the causative organism the differential diagnosis is most difficult. Not only are the neurological features similar, but the association of pulmonary and central nervous system torulosis (about 1 in 5) provides another similarity and, hence, another obstacle. The x-ray appearance of pulmonary torulosis was reviewed by Greening and Menville (18), who found that in early lesions the chest plate is fairly characteristic. Torula tends to involve the bases of the lungs (but may occur in the apices) and the densities are more sharply demarcated than those produced by tubercles. Older lesions usually become confluent, however, and there may be cavitation, miliary spread, or healing by fibrosis. Torulas have been found in sputum (the Ziehl-Neelsen stain demonstrates torula and tubercle bacilli equally well), but patients with respiratory involvement rarely have a productive cough.

A clinical course suggesting intracranial tumor has been reported several times (6, 19), as papilledema is a frequent finding. This was also true of the two cases reported herein. In Case 1, the clinical features justified, certainly in the early phase, a diagnosis of posterior fossa tumor. This was supported by the cerebrospinal fluid findings and ventriculography. As the pleocytosis made its appearance tuberculous meningitis was thought of as a strong possibility, but not to the full exclusion of a posterior fossa neoplasm. Significantly enough, a biopsy failed to establish the diagnosis, although this is a method which should give at

least a diagnostic lead (20). The second case presented problems in diagnosis not unlike those encountered in Case 1.

Therapeutic measures. Patients with torulosis of central nervous system have been treated with a variety of therapeutic agents. In no instance was there established permanent cure. Even the few who had an extended survival period were not well; in the preponderant number of instances a fatal outcome occurred within 6 months of the onset of symptoms.

A notable exception is the patient of Reeves, Butt and Hammack (21), who was living, but not well, 7 years and 8 months after diagnosis [according to the follow-up reported by Voyles and Beek (16)]. On the other hand, many hyperacute cases have been reported. Piper's (22) patient, for example, died within 11 days of onset.

No consistent results, either *in vivo* or *in vitro*, have been obtained with *sulfonamides* (18, 22, 23, 24, 25, 26, 27, 28, 29, our Case 1), *iodides* (12, 18, 24, 30, 31), *arsenicals* (8, 12), *colloidal silver* (30), *colloidal copper* (32), *tartar emetic* (9), *mercurochrome* (9), *quinine* (30), *tricrosol* (30), *tyrocidin* (18), *gentian violet* (27, 32), *thymol* (27), *streptomycin* (33, 34, 44), *autogenous vaccine* (35), *methenamine* (32), *intravenous alcohol* (36), *gold sodium thiosulfate* (32), or *aeriflavin* (37). Krainer, Small, Hewlitt and Deness (38), using the organism from their own case, and Hobby, Meyer and Chaffee (39), found torula to be susceptible to penicillin *in vitro*. Hamilton and Thompson (25) succeeded in reducing the cerebrospinal fluid parasite count from 1200 to 7 per cc. by the use of intrathecal penicillin; their patient subsequently died, but permission for autopsy was not obtained. Most investigators, however, have found penicillin to be ineffective, both *in vivo* and *in vitro* (7, 18, 27, 40, 41). Goldberg (42) gave large doses of vitamin D for 5 months, at the end of which time there was considerable clinical improvement. In spite of continued treatment, the patient later relapsed. Stone and Sturdivant (32) found x-rays effective in inhibiting the growth of torula in culture, but the effect of radiation in their patient, our Case 2, and the patient of Warvi and Rawson (43) was questionable.

Further investigation seems to be desirable along lines suggested by the work of Kuhn (10). He noted the resistance of rabbits to experimentally induced torula infection, contrasted with the high susceptibility of mice. He measured the normal body temperature of groups of these 2 animals, and found that mice have an average temperature of 99.1°F. (37.3°C.) and rabbits, 103.15°F. (39.5°C.). He also found that sustained temperatures of 105° and 107°F. (40.5° and 41.7°C.) over a period of a week killed cultures of torula. It is well known that torula infection rarely produces high fever. This fact, in the light of the work of Kuhn, would suggest that hyperthermia might be used as a method of treatment. This theory, however, loses some of its appeal in view of the observations of Cox and Tolhurst (7) that the few patients reported with high fevers died more rapidly than the average case. Furthermore, rabbits that contract torulosis through experimental inoculation also die faster. Hyperthermia has not yet been used in human torulosis, and in view of the uniformly hopeless prognosis, it seems worth trying, despite these theoretical objections.

Robinson, Smith and Graessle (33); Waksman (34); and Reilly, Schatz and

Waksman (44) reported the results of inhibition studies of several antibiotic substances against *Torula*. Streptomycin was ineffective, and several other products were effective but highly toxic for animals. *Streptothricin*, however, was found to inhibit growth in concentrations which can be obtained in body fluids, including the cerebrospinal fluid; its absorption, excretion and distribution are roughly similar to that of streptomycin (45). The toxicity of streptothricin has not been fully studied, but what evidence is available unfortunately points against its clinical usefulness (46, 47), particularly in the central nervous system (48). It is possible that the high toxicity of streptothricin is caused by impurities (46), although this, too, has been questioned (47). It has not yet been used against this disease, as far as we know, either in animals or humans.

SUMMARY

1. Two cases of torulosis of the central nervous system are reported.
2. The difficulties in diagnosis are emphasized and effective diagnostic steps are listed.
3. The biologic characteristics of the causative organism are reviewed.
4. The histopathologic alterations in the nervous system are described.
5. Therapeutic measures are discussed and evaluated.

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The foregoing list of references is selected from a voluminous literature on the subject. Included are the excellent and comprehensive reviews by Levin (2), Blair (9), Binford (13), Voyles and Beck (16), Reeves, Butt and Hammack (21), Freeman (49), and Debré (50). Particularly complete is the recent monograph of Cox and Tolhurst (7).

PROLONGED MODERATE DOSE THERAPY VERSUS INTENSIVE SHORT TERM THERAPY WITH PENICILLIN AND CARONAMIDE IN SUBACUTE BACTERIAL ENDOCARDITIS*

FREDERICK H. KING, M.D., S. STANLEY SCHNEIERSON, M.D., MARCY L. SUSSMAN, M.D., HENRY D. JANOWITZ, M.D. AND GENE H. STOLLERMAN, M.D.

From the Medical Services and the Department of Bacteriology Laboratories of The Mount Sinai Hospital, New York

Since the introduction of penicillin in the treatment of subacute bacterial endocarditis, numerous reports have been published of results achieved and dosage schedules employed. Out of the large experience which followed the initial favorable reports, two features of therapy emerged as vital to success. It was emphasized that sufficiently high dosage be used to insure a high enough blood and tissue level in relation to the resistance of the causative organisms. Thus, many authors advocated the maintenance of a blood level of 5 to 10 times the amount of penicillin necessary to inhibit the growth of the causative organism *in vitro*. It was also advocated that to insure thorough sterilization of the blood and especially of the vegetations, treatment must be continued for a minimum of 4 to 6 weeks. Although occasional successes were reported with short term therapy, the longer regime was urged as a general treatment schedule by a majority of investigators.

In a previous publication (1) we reported a method for achieving high blood penicillin levels by rapid, frequently repeated intravenous injections of large doses of penicillin, using caronamide (2) as an adjuvant to block tubular excretion of the antibiotic. This method offered an opportunity for possible re-orientation with respect to dosage and duration of treatment. Following the suggestion by Gerber, Schwartzman and Baehr (3) that high peak levels of penicillin resulted in better penetration into infected foci, it seemed a justifiable presumption that the maintenance of extremely high levels of penicillin might reduce the necessary treatment period and the risks attendant upon prolonged disease.

To test the effectiveness of intensive treatment a series of eight typical cases of subacute bacterial endocarditis was treated by the method of massive short term therapy with penicillin and caronamide. In each case the period of treatment was completed within 10 days or less. The regime consisted in almost all instances of giving penicillin and caronamide† as follows: For 10 days the patient received a daily series of 10 rapid intravenous injections of 1,000,000 units of penicillin at hourly intervals. This was given in the form of crystalline penicillin G dissolved in 5 cc. of distilled water. It was found most feasible to inject

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† Kindly supplied by the Sharpe and Dohme Co.

this through the rubber tubing or directly through the indwelling needle of an intravenous set while the patient was receiving a slow drip infusion of 5 per cent glucose in distilled water during the 10 hours. To prevent excessive drop in the blood penicillin level during the remaining 14 hours of the day, the patient, in most instances, received 4 intramuscular injections of 1,000,000 units of penicillin at equal time intervals during this period. Thus in each case, except one, the patient received 14 million units of penicillin in 24 hours and a total of 140 million units during the course of ten days. Caronamide was usually given by mouth in doses of 4 grams every 3 hours day and night for 24 hours before beginning penicillin therapy and its administration was continued throughout the 10 day course. In 2 instances where the patient was unable to tolerate the medication when given orally, an appropriate preparation was administered intravenously in doses of 3 grams every 6 hours.

CASE REPORTS

Case 1. The patient (B. B.) was a white woman, aged 27 years, with long standing rheumatic cardiorvalvular disease affecting the mitral and aortic valves. Her recent symptoms began 2 months before admission. She complained of fever, malaise, cough and tender red spots on her fingers. The pertinent physical findings included evidence of mitral stenosis and mitral and aortic insufficiency, pallor, a tender red spot on the tip of the right fourth finger, a tender erythematous area on the palm of the left hand and clubbing of the fingers. There was electrocardiographic evidence of auricular fibrillation and there were present clinical evidences of mild congestive failure. The patient was febrile. She was moderately anemic. The blood culture revealed 30 colonies per cc. of *Streptococcus viridans*. This organism was 15 times as resistant to penicillin as the standard *Staphylococcus aureus* H employed in this laboratory.*

Three weeks before admission to the hospital the patient received 2 injections of 300,000 units of penicillin in oil and beeswax. At this time she also received 1 gram of sulfadiazine orally every 4 hours for 9 days.

The congestive failure was successfully treated with digitalization, salt restriction and mercurial diuresis. The patient was then given massive penicillin therapy for one day. This consisted of 10 rapid, hourly injections of crystalline penicillin G dissolved in distilled water. Caronamide was given for 24 hours before, and then during, the administration of the antibiotic. This was given orally in doses of 4 grams every 3 hours.

Penicillin blood levels** were determined at frequent intervals during the course of treatment and are given in detail in this case to demonstrate the levels which may be maintained by this method. The levels obtained at various times after injection were as follows:

* The resistance to penicillin was determined by comparing the amount of penicillin required to inhibit the growth in vitro of a suitably diluted inoculum from a six hour culture of the organism under test as compared with the amount of penicillin required to inhibit a similar inoculum of the standard organism, *Staphylococcus aureus* H. The amount of penicillin required to inhibit the test organism divided by the amount required to inhibit the standard organism was the penicillin resistance expressed as the coefficient of resistance, compared with the *Staphylococcus aureus* H standard. The standard organism was inhibited by 0.02 units per cc.

** The method of penicillin assay employed is a broth tube dilution method using *Staphylococcus aureus* H as the test organism and fresh meat extract broth as the medium. The minimal concentration of the standard penicillin required to inhibit the inoculum of 5×10^2 *Staphylococcus aureus* H cells was 0.02 units per cc. The standard penicillin was obtained from the U. S. Department of Agriculture. All titrations of serum levels were accompanied by, and compared with, this standard.

TIME DOSE	SERUM LEVEL (units/cc)
5 minutes after first million units.....	184
15 minutes after first million units.....	120
30 minutes after first million units.....	88
55 minutes after first million units.....	64
5 minutes after fifth million units.....	228
15 minutes after fifth million units.....	176
30 minutes after fifth million units.....	144
55 minutes after fifth million units.....	96
5 minutes after tenth million units.....	256
15 minutes after tenth million units.....	240
30 minutes after tenth million units.....	240
55 minutes after tenth million units.....	200

Twenty-four hours after completion of this course of penicillin the patient's temperature was normal for the first time in four weeks. Forty-eight hours later it had returned to its pre-treatment level. A blood culture at this time revealed 8 colonies per cc. of *Streptococcus viridans*, whose resistance was unchanged. Therefore it was decided to treat the patient for 10 days. Caronamide was resumed one day before penicillin treatment was reinstituted and was continued for the next 10 days. For ten successive days the patient received 10 hourly intravenous injections of 1,000,000 units of crystalline penicillin G dissolved in 5 cc. of distilled water. In this case no penicillin was given during the remaining 14 hours of the day. Penicillin blood levels, taken at random during this period, were similar to the high levels detailed above. The lowest levels ranged from 5.7 units per cc. (at 13 hours after the last intravenous injection), to 64 units per cc. (at 55 minutes after an intravenous injection).

By the 7th day the patient's temperature had progressively declined to normal levels. On the 8th day there was a rise in temperature coincident with a phlebitis of the left antecubital veins. On the day following the completion of therapy the patient's temperature was again normal and the blood culture was sterile. The patient's general condition improved. During the six weeks following cessation of treatment weekly blood cultures were negative and the patient was discharged from the hospital. It is now 6 months since treatment was discontinued and the patient is clinically well.

Comment. This was the first case in which massive short term therapy resulting in sustained high penicillin blood levels was applied. An effort to achieve sterilization with treatment for one day failed. Subsequently, the administration for 10 successive days of 10 hourly intravenous injections of 1,000,000 units of crystalline penicillin in conjunction with caronamide resulted in the successful sterilization of the blood stream and vegetations. The patient has remained clinically cured of bacterial endocarditis for over 6 months.

Case 2. This patient (D. F.) was a young man aged 30 years, who was said to have acquired a murmur at the age of 4 years following scarlet fever. Four weeks before admission he developed chills, sweats, weakness and fatigability. The patient had a temperature of 101.2° F. on admission. The heart was enlarged to the left and a harsh, crescendo murmur was audible at the apex. There was clubbing of the fingers and toes. Painful Osler nodes were present on the thumb and 5th finger of the left hand. The spleen was palpable two fingerbreadths below the left costal margin. There was present a moderate anemia, a leucocytosis and a shift to the left on differential count. A diphtheroid *Streptococcus viridans* was grown in a blood culture, varying from 10 to 40 colonies per cc. This organism was equal in penicillin sensitivity to that of the standard organism.

The first course of therapy was given for 5 days and consisted of the usual 10 million units a day, divided into hourly injections of a million units each, and 4 intramuscular injections of the same dose every night. This was accompanied by the administration of caronamide in the usual amounts. The highest blood level achieved during this period was 200 units per cc. in a sample obtained 5 minutes after the 5th intravenous injection of the first day. The lowest level was 33.3 units per cc. in a sample taken 13 hours after the last intravenous injection of the first day. A blood culture taken on the completion of treatment was found to be positive.

The patient was then given a ten day course of the same treatment, the total dose for the course being 140 million units. During this period the highest penicillin level attained in the blood was 260 units per cc. (in a sample obtained 10 minutes after the last intravenous injection of the 10th day), and the lowest level found was 10 units per cc. (obtained 13 hours after the last intravenous injection). On completion of this course the blood culture was sterile, but was positive again one week later.

Following this failure the patient was given 400,000 units daily in divided doses for two weeks by the intramuscular route. The blood culture remained positive and the dose per day was increased to 800,000 units. Although this treatment was continued for 5 weeks, the blood culture at the end of that time was still positive.

It was decided at this point to use streptomycin. The resistance of the organism to streptomycin was 4 times that of the standard. Four grams per day were given for three days following which the patient received 2 Gm. per day for 7 days. At the conclusion of this therapy the blood culture was negative. At this juncture penicillin treatment was reinstituted. Crystalline penicillin G was given by continuous intravenous infusion for eight weeks at the rate of 800,000 units per day. The blood culture remained negative during this treatment and was negative at its termination. The patient seemed to be clinically recovered and was discharged from the hospital. When seen in the Follow-up Clinic five months after discharge he was well and the blood culture was negative.

Comment. In this case two attempts with massive short term therapy, one for a period of 5 days and another for 10 days, failed to sterilize the vegetations. Prolonged treatment for 5 weeks with smaller doses likewise proved ineffectual. The blood culture became consistently negative only when streptomycin was given. Sterilization was maintained with penicillin. Clinical cure was therefore achieved by the use of a combination of antibiotics, streptomycin being employed for a relatively short time and penicillin for a protracted period.

The experience in this case emphasizes the significance of the time factor in the penicillin therapy of subacute bacterial endocarditis. It also illustrates the fact that determination of the sensitivity of the organism within the usual low ranges does not necessarily give a clue to the ease or difficulty of effecting sterilization. In this instance the organism was a very sensitive one, yet it required prolonged treatment ultimately to cure the patient.

Case 3. The patient (R. H.) was a white man, aged 65 years, who became ill 3 months before admission, complaining of weakness, anorexia and weight loss. He was hospitalized for a short time at another institution, where he received penicillin. The amount given could not be ascertained. The pertinent findings on admission were fever, ecchymoses over the left eye, a left subconjunctival hemorrhage, a petechia in the left lower conjunctiva, a harsh apical systolic murmur transmitted to the axilla, early clubbing of the fingers, a palpable spleen and anemia. Two blood cultures yielded a non-hemolytic *Streptococcus salivarius*, having 10 times the resistance of the standard organism.

Administration of penicillin was begun following preparation with caronamide for 24 hours. This was continued throughout the period of administration of penicillin which

was given as outlined, viz., 1,000,000 units intravenously every hour for 10 doses during the day and 1,000,000 units intramuscularly 4 times during the night, giving a total dose of 140 million units. During this period the blood levels in samples obtained 14 hours after the last intravenous injection were lowest and ranged between 13 and 40 units per cc. The peak levels in blood samples obtained 5 minutes after an intravenous injection ranged between 180 and 240 units per cc.

On the second day after beginning treatment the temperature dropped to normal and remained normal except for a temporary elevation associated with mild thrombophlebitis. A blood culture taken one day after completion of the course was negative. However, four days later the patient began to run a low grade fever. Six days later the blood culture was once again positive, revealing the same organism with resistance unchanged.

Penicillin therapy was reinstituted. The drug was now given in doses of 50,000 units every 3 hours by the intramuscular route. This was continued without interruption for 34 days. The patient's temperature fell to normal soon after treatment was resumed and remained normal thereafter. His general condition improved. The cardiac murmur became softer and the spleen became impalpable. Blood cultures at weekly intervals were negative. The patient was discharged two weeks after treatment was stopped. He was last seen in the Follow-up Clinic five months after discharge and was found to be clinically well, without any evidences of sepsis. A blood culture was not obtained at that time.

Comment. Penicillin in massive doses for a ten day period, given in conjunction with caronamide, resulted in sustained high levels in the blood but failed to achieve a cure of the infection. In contrast, administration of penicillin in much smaller dosage over 34 days resulted in sterilization and apparent cure.

Case 4. The patient (E. B.) was a white man, aged 51 years, with a history of continued illness for about a year and a half. During this period he had persistent fever, weakness and anorexia. On one occasion a blood culture was positive for *Streptococcus viridans*. The patient was given a number of courses of penicillin during his illness but the exact amounts given and the duration of the courses could not be ascertained. However, the approximate amount of penicillin administered during the 18 months was said to be about 300 million units. Each time the antibiotic was administered the fever subsided, only to recur about 10 days after the drug was stopped. The patient also received one course of streptomycin but the amount given and the duration of the course were unknown. He was admitted to the hospital because of the failure of previous treatment to cure the infection.

The pertinent findings were fever; a short presystolic and a long, blowing, systolic murmur at the apex; a harsh systolic murmur over the pulmonic area; a palpable spleen; suggestive clubbing of the fingers; albuminuria and microscopic hematuria; and moderate anemia. A blood culture disclosed 36 colonies per cc. of *Streptococcus viridans* having 5 times the resistance of the standard organism.

This patient, like the others, was placed on a ten day course of treatment with crystalline penicillin and caronamide. He received 1,000,000 units of penicillin intravenously every hour for 10 hours daily and 1,000,000 units intramuscularly 4 times each night. Caronamide was given orally in doses of 4 grams every 3 hours throughout the ten day period as well as for 24 hours preceding administration of penicillin. During the treatment the lowest blood level obtained in a sample drawn 13 hours after the last intravenous injection of the 10th day was 20 units per cc. The highest level, found 10 minutes after the 10th injection of the first day, was 460 units per cc.

On this regime the temperature promptly fell to normal levels, the spleen became smaller and several blood cultures at the end of the course were negative. The patient was discharged from the hospital and to the care of his private physician. Within two weeks, however, the temperature was again elevated and the blood cultures again became positive. The patient has been placed, and will continue for an indefinite period, on a regime of

300,000 units of procaine penicillin twice daily. On this schedule he has remained symptom free and afebrile.

Comment. In this case massive penicillin therapy for 10 days together with caronamide failed to accomplish persistent sterilization. The unusually prolonged and irregular employment of penicillin before massive therapy was attempted had likewise been futile. Present therapy at home with moderate doses has not yet proved effectual although it has already been carried out for several months.

The failure of all therapy to sterilize the vegetations infected with a relatively sensitive organism strongly suggests that microorganisms are present within the depths of partially organized vegetations and that the drug fails to penetrate to these bacteria. High peak levels are apparently no more effective, in this case, in achieving penetration.

Case 5. The patient (M. K.) was a white male, 27 years of age, who complained of low grade fever and malaise for 4 weeks before admission. Because the fever failed to respond to bed rest and aspirin, his physician gave him a six day course of daily injections of 300,000 units of procaine penicillin. The temperature declined on the second day of the treatment and remained normal for a week. Afterwards he again became weak and feverish and was admitted to the hospital.

The findings of significance were fever, a harsh systolic murmur at the apex with an accentuated first sound, a harsh systolic murmur at the base transmitted to the neck, a systolic thrill and a high-pitched diastolic murmur over the latter area and mild anemia. The blood culture grew out *Streptococcus viridans*, 200 colonies per cc., with a resistance five times that of the standard organism.

The patient was given the ten day course of penicillin. He received 1,000,000 units intravenously every hour for 10 hours during the day and one million units 4 times during the night intramuscularly. Caronamide was given orally, 4 grams every 3 hours, for 24 hours before penicillin was started and was continued throughout the next ten days of treatment. On this regime the lowest blood levels ranged from 6.6 to 20 units per cc. (in samples taken 3 hours after the last intramuscular injection), and peak levels of 66 to 133 units per cc. were obtained in samples taken 5 minutes after the last intravenous dose.

The temperature fell to normal on the second day of this therapy and remained normal for the duration of the treatment. Blood cultures during the course and on the last day of treatment were sterile. However, one week later the blood culture was again positive for the same organism, whose resistance *in vitro* to penicillin was unchanged.

The patient was then given a course of therapy for six weeks consisting of the intramuscular injection of 450,000 units of procaine penicillin every 12 hours. The blood levels ranged from 0.68 to 2 units per cc. The temperature promptly fell to normal and remained normal thereafter. Repeated blood cultures during treatment and on discharge were negative. The patient appeared better clinically as far as the infection was concerned, but the aortic insufficiency became more marked. Four weeks after discharge from the hospital he was free of all evidence of sepsis and congestive failure; the blood culture was negative. He was clinically well when last seen in the Follow-up Clinic 3 months after treatment was stopped.

Comment. This patient's illness was not significantly influenced by massive penicillin therapy for 10 days. While it succeeded, as it usually does, in temporarily sterilizing the blood stream, it obviously failed to sterilize the vegetations, since the blood culture was positive within a week after treatment was stopped. The prolonged administration of procaine penicillin, resulting in levels

ranging from 0.68 to 2 units per cc., succeeded in achieving sterilization and clinical cure, whereas massive doses over a short period, yielding concentrations of 6.6 to 133 units per cc., failed.

Case 6. The patient (A. K.) a white man, aged 47 years, became ill 5 weeks before admission. He developed fever, headache and malaise. His physician suspected virus pneumonia. The patient received penicillin but the amount could not be ascertained. Upon discontinuing penicillin the temperature rose again and was uninfluenced by salicylates or sulfonamides. The patient was therefore hospitalized.

The significant findings were fever; a petechia on the right buccal mucosa; enlargement of the heart to the left; a systolic murmur at the apex; early clubbing of the fingers; erythematous, indurated, slightly tender nodules on the extensor surfaces of the arms and legs; and moderate anemia. Two blood cultures disclosed *Streptococcus salivarius*, 8 and 11 colonies per cc. This organism had one-half the resistance to penicillin of the standard organism.

The patient was then given massive penicillin therapy in conjunction with caronamide. He received a 10 day course of 1,000,000 units intravenously every hour for 10 doses during the day and 4 doses of 1,000,000 units intramuscularly each night. Caronamide was given orally in doses of 4 grams every 3 hours for 24 hours before penicillin treatment was begun. He did not tolerate this and was given 3 grams of the drug by the intravenous route until the end of the course. On this regime the lowest penicillin blood level was 11 units per cc. (in a sample obtained 3 hours after the last intramuscular injection), while the peak level was 132 units per cc. (at 5 minutes after the last intravenous injection).

Ten days after therapy was begun the patient was subjectively better. There was a gradual decline in temperature, which was normal by the 8th day. During the next two weeks the patient remained afebrile and two blood cultures were sterile. However, after two weeks the blood culture again showed *Streptococcus salivarius*. The patient was then placed on a regime of 450,000 units of procaine penicillin every 12 hours which he received for 6 weeks. It is now 2 months after treatment was discontinued and he appears clinically well. Weekly blood cultures taken during the treatment period were consistently negative.

Comment. In this case massive penicillin therapy for 10 days with the aid of caronamide failed to sterilize in spite of the fact that the infection was a relatively recent one and the organism was very sensitive to penicillin. However, with prolonged low dosage therapy the infection has apparently been controlled.

Case 7. The patient (O. E.) was a white man (a dentist), aged 48 years, with a five month history of recurring joint pains associated in some instances with swelling and redness. He had noted low grade fever during the past several months. One month before admission he developed persistent tachycardia. Because of this and the continued fever he was referred to the hospital. Five weeks before admission he received penicillin for several days but the amount was not definitely known.

The pertinent findings were fever, tachycardia (144 beats per minute), slight enlargement of the heart to the left, poor heart sounds, soft apical and basal systolic murmurs and mild anemia. It was thought at first that the patient had rheumatic fever but the blood cultures repeatedly showed a nonhemolytic diphtheroid *Streptococcus* varying from 36 to 60 colonies per cc. This had the same resistance as the standard.

The patient, like the others, was treated for ten days with 14 million units of crystalline penicillin G daily, given in hourly doses of 1,000,000 units intravenously during the day for 10 doses and 1,000,000 units intramuscularly every 4 hours during the night for 4 doses. Simultaneously he received caronamide. Since he could not tolerate the drug orally, it was given intravenously in doses of 3 grams every 6 hours. On this program the penicillin blood levels varied from a low of 4.4 to 11 units per cc. (in samples taken 3 hours after the last

intravenous injection), to peak levels of 160 to 340 units per cc. (in samples obtained 5 minutes after the last daily intravenous injection).

Three days after this course of therapy the blood culture was sterile. However, the temperature rose again and on the 10th day after the completion of the course the blood culture again showed the same organism with its resistance unchanged.

The patient was then started on routine therapy of 50,000 units intramuscularly every 3 hours. This was continued for 36 days. Repeated blood cultures during this period and for two weeks afterward were negative. At the end of that time the blood culture was found to be positive once again. He was now given 2 grams of streptomycin daily for a week and the blood culture became sterile. This was followed by 300,000 units of penicillin in oil and beeswax daily. It was intended to maintain this program uninterruptedly for 7 weeks. However, after 5 weeks the blood culture was positive and the dose was increased to 300,000 units procaine penicillin twice daily. It is intended that this be continued for an indefinite period. At this writing, after 2 weeks of procaine penicillin, the blood culture still contains non-hemolytic diphtheroid *Streptococcus*.

Comment. This patient was given massive penicillin therapy for a ten day period without result. Routine treatment with lower doses for prolonged periods and treatment with streptomycin for a short time have thus far failed to accomplish sterilization. The organism was identical with that isolated in case 2 of this series. In this case it was as sensitive to penicillin as the standard organism; yet the infection has withstood prolonged therapy with penicillin including a short period of streptomycin. The case therefore serves as another illustration of the fact that in subacute bacterial endocarditis the sensitivity of the organism may not be a sure guide to dosage schedule and carries with it no prognostic implications.

Case 8. A white man, (H. S.), aged 25 years, had a long standing history of heart disease. About three weeks before admission to the hospital, following dental treatment, the patient noted the gradual onset of weakness and fatigue. Two weeks before entering the hospital he developed a shaking chill, drenching sweats, nausea and vomiting. During the week before admission he was treated at another hospital with penicillin injections every 4 hours for 4 days but the amount was not known. He continued to have chills and fever and was transferred to the Mount Sinai Hospital.

The patient was acutely ill and febrile. He had white-centered petechiae on the soft palate, left lower conjunctiva and upper lip. The heart was enlarged to the left. There were systolic, diastolic and presystolic murmurs at the apex. An aortic diastolic murmur was also present. There was clubbing of the fingers. An Osler node was noted on the terminal phalanx on the left third finger. The patient was mildly anemic. The first blood culture was negative but the second one contained 16 colonies per cc. of *Staphylococcus albus* B. This organism had the same resistance to penicillin as the standard organism.

The patient was given a ten day course of penicillin consisting of hourly intravenous injections of 1,000,000 units of crystalline penicillin G for 10 doses during the day and 4 intramuscular injections of 1,000,000 units at night. Caronamide was administered during the day before penicillin was begun and was then continued during the course of treatment. It was given intravenously in doses of 3 grams every 6 hours. Low penicillin levels in the blood ranged from 5 to 20 units per cc. in samples obtained 3 hours after the intramuscular injection. The peak levels attained at 5 minutes after an intravenous injection ranged from 22 to 80 units per cc. The patient's temperature continued to spike to 104° and 105° F. during the first 6 days of the treatment and fell to slightly lower levels during the last 4 days. On the 5th day a blood culture was negative. Yet he continued to run a fever and had an elevated temperature after completing the course of intensive treatment. The

patient was therefore placed on routine dosage of 50,000 units intramuscularly every 3 hours. This was continued for 34 days. Within 4 days the fever began a downward trend and soon reached normal levels where it remained, except for occasional rises to 101° F. during the next two weeks. At this point, however, the patient developed evidences of congestive failure as well as severe thrombophlebitis of the right calf. The evidences of sepsis disappeared but the patient succumbed to congestive heart failure.

At post mortem examination there was found rheumatic valvulitis of the mitral valve with superimposed subacute bacterial endocarditis. The chordae tendineae of the mitral valve were ruptured. Infarcts were present in the kidney and spleen. *Staphylococcus albus* B was recovered on culture of the vegetations of the mitral valve.

Comment. In this early case of subacute bacterial endocarditis short term intensive penicillin therapy in conjunction with caronamide failed to influence the clinical course beneficially. Sterilization of the blood may have been achieved during the intensive treatment but the post mortem findings indicate that it failed to sterilize the vegetations. Whether sterilization could ultimately have been secured with continued treatment at lower dosage, had heart failure not supervened, can only be conjectured.

DISCUSSION

In the foregoing investigation, in order to test the effectiveness of massive short term therapy, a very high level of penicillin was maintained for 10 days in the blood and, presumably, the body fluids. In spite of very high blood penicillin levels, the infection persisted in 7 out of the 8 cases. This represents a bacterial cure in only 12.5 per cent as compared with an overall cure rate variously reported as between 70 and 80 per cent (4). Since the latter figure includes deaths both from heart failure and from other causes, the bacterial cure rate must be even higher. Evidently massive short term therapy is not as effective as the conventional methods of treatment. As further evidence of the superiority of conventional therapy, 4 out of the 7 failures were subsequently cured by prolonged treatment with moderate doses. In one additional instance where massive therapy failed, the patient died in congestive failure with the infection apparently controlled after 34 days of low dosage treatment. At autopsy, however, culture of the vegetations revealed the same organism that was isolated from the blood during life. It is a matter of speculation whether more prolonged therapy might ultimately have succeeded in this case as well, had not heart failure terminated the illness.

Out of this experience, several provocative speculations arise regarding possible factors involved in the effective treatment of subacute bacterial endocarditis. Discussion will be limited to the following considerations: (1) optimal concentration of penicillin in the blood and tissues, (2) duration of treatment, (3) the nature of the pathologic lesion, and (4) resistance of the causative organism.

With reference to the question of optimal concentration of penicillin in the blood, the possibility arises that the high levels achieved during short term therapy were actually detrimental. Eagle has demonstrated (5, 6) that the susceptibility of a given organism *in vitro* may be defined in terms of three con-

centrations. The first is that which is just enough to reduce the normal rate of multiplication. Just above this is the concentration in which the organisms are killed faster than they multiply, so that there is a gradual decrease in the number of viable organisms. The third zone of concentration is that in which the organisms are killed at a maximal rate and may be regarded, therefore, as the optimum zone. With some strains of Streptococci and Staphylococci this optimum zone is sharply defined. Paradoxically, certain microorganisms, when exposed to concentrations in excess of optimum, are killed at a *slower* rate.

It is conceivable that with the regime of intensive therapy the causative organisms were consistently exposed to a concentration of penicillin in this so-called "paradoxical zone." Cases 4 and 7 indicate that lower levels do not necessarily result in cure even when treatment is prolonged, but these levels might not have been optimum.

With respect to duration of treatment, the recent observations of Spicer and Blitz (7) are important. They observed that "the success of penicillin therapy depends directly on the number of residual organisms left viable after the initial treatment with penicillin. The very small numbers of residual viable organisms in strains of Pneumococcus, hemolytic Streptococcus and some strains of Staphylococcus, shown by our tests, may account for the dramatic results so often obtained in penicillin when used in the treatment of acute infections caused by these organisms. On the other hand, the very large numbers of viable organisms found in Streptococcus viridans strains as our tests indicate may account for the protracted treatment with penicillin necessary in cases of subacute bacterial endocarditis in which Streptococcus viridans is the most frequent etiological agent."

Spicer and Blitz (7) also noted that *in vitro* the residual bacteria were frequently destroyed by streptomycin. In respect to this observation our Case 2, which was treated before appearance of the report of Spicer and Blitz, may be of some interest. Cure in this case could not be achieved either with massive short term therapy or with long term therapy with moderate dosage. However, the administration of streptomycin for 7 days immediately following the course of penicillin resulted in a negative blood culture. A further course of penicillin was then given for 8 weeks and the patient made a clinical recovery.

The possibility exists that short term therapy does not allow for thorough penetration of the focus of infection. There is basis for this belief in the fact that during the treatment period and for a short time thereafter the blood cultures were sterile. It would seem, as others have conjectured, that those organisms in contact with penicillin, being susceptible, are destroyed. The survivors in the depths of the vegetations presumably proliferate on discontinuance of therapy, to be later discharged into the blood stream.

The character of the pathologic lesion probably influences long term therapy as well. In one case in this series (Case 4) irregular employment of penicillin for 1½ years, then massive therapy for a short period, followed by routine therapy for over 5 months has resulted consistently in sterilization of the blood during treatment periods, only to have sepsis recur after discontinuance of therapy.

It is probable that in this case partially healed vegetations prevent thorough penetration by the antibiotic. However, prolonged treatment offers a better opportunity for ultimate penetration of the vegetations and probably accounts in part for what appears to be a much higher incidence of success than obtains with short courses of therapy.

Failure with massive therapy can not be attributed to high resistance of the infecting organisms. None of the cases was caused by such highly resistant organisms as the enterococcus or *H. influenzae*. The infecting organisms in our series had an *in vitro* resistance of 0.5 to 15 times that of the standard organism, which is considered to be well within the susceptible therapeutic range.

Within the range of resistances encountered in this series there was no relation between the amenability of the infection to control and the degree of resistance of the organism. Thus, the only infection (Case 1) which was controlled with short term therapy was produced by the most resistant organism in this group; while Cases 2, 4 and 7, which resisted control even when exposed to prolonged and presumably adequate therapy, were caused by very sensitive microorganisms. This is in keeping with the experimental experience of MacLeod (8), whose findings in *Pneumococcus* infections in mice are evidence against transferring *in vitro* results to *in vivo* conditions. It is also in harmony with the clinical experience of Christie (9), who found in a large series of cases in various centers in Britain, that the percentage of relapses and deaths with infection uncontrolled did not appear to be related to the resistance of the organisms.

SUMMARY

Of 8 cases of subacute bacterial endocarditis, only one was cured by the maintenance of very high penicillin levels in the blood for 10 days. Four of the remaining 7 were subsequently cured by prolonged moderate dose treatment. The superiority of prolonged treatment over short term intensive treatment is thus indicated.

Several theoretical considerations regarding the possible reasons for the superiority of long term therapy in subacute bacterial endocarditis are discussed.

Within the range encountered in this series there was no correlation between the degree of resistance of the organism *in vitro* and the ease or difficulty of clinical control of the infection.

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MORPHOLOGIC EFFECTS OF STILBAMIDINE

REPORT OF AUTOPSIES IN THREE STILBAMIDINE-TREATED CASES

MILTON KANNERSTEIN, M.D.¹

Since 1939 a group of drugs designated as aromatic diamidines, of which 4:4-diamidinostilbene (stilbamidine) and 4:4-diamidinodiphenoxypentane (pentamidine) are the outstanding ones, have been used successfully in the treatment of kala-azar and trypanosomiasis (1 to 6).

Recently Snapper (7) has used these drugs in the treatment of multiple myeloma with relief of pain and apparent temporary arrest of the malignant process. On the basis of *in vitro* antibacterial activity, Rosenberg (8) tried stilbamidine in 6 patients with rheumatoid arthritis without apparent effect.

There have been a number of pharmacologic studies of these drugs in laboratory animals (9 to 13). Their use in cattle and horses has also been reported from British Colonial centers in Africa where domestic animal infections are a serious problem (14 to 17). Microscopic findings in tissues of these animals have been recorded in only a few instances. In one of the earliest reports Adler and Tchernomoretz (9), using Syrian hamsters who had been given a single lethal dose of stilbamidine, describe desquamation of the renal tubules, especially the convoluted, widening of the glomerular capillaries, and congestion of the liver with irregular patches of fatty degeneration.

Kirk and Henry (18) in discussing the toxicity of stilbamidine describe in some detail the histology of the kidney and liver in animals poisoned by a single large or smaller repeated doses. The kidneys showed intense congestion and all degrees of "tubular nephritis." Focal hemorrhages were present in the medulla and intermediate zone. Cells of the convoluted tubules and loops of Henle showed all degrees of injury from cloudy swelling to necrosis. The glomeruli were never affected to the same degree as the tubules. In the liver there was congestion with distention of central veins and sinusoids. What was considered fatty degeneration was the most constant and typical finding in the liver, being patchy sometimes, and in some cases universal. However these were not typical fat vacuoles in appearance and the authors did not have the facilities to do staining for fat. In this paper Kirk and Henry give the only discoverable description of pathologic changes in some human cases who were believed to have died as a result of *diamidine* intoxication; they were believed to have been treated by bottled, light-exposed solutions.

Daubney and Hudson (14) investigated the action of stilbamidine and pentamidine on cattle with experimental *Trypanosoma congolense* infections. A few of the animals died a number of days after a series of injections of pentamidine. The liver of these animals showed advanced fatty degeneration. The kidneys in one case only showed slight swelling of the cells of Bowman's capsule and the tubules. No lesions attributable to the drug were found in stilbamidine-treated animals.

¹ George Blumenthal, Jr., Fellow in Pathology, Mount Sinai Hospital, New York.

In man, in general, toxic reactions have not been a serious problem. With the conventional therapeutic dosage immediate reactions consist of a fall in blood pressure and a series of subjective symptoms; no immediate fatalities or other serious consequences have been reported (1a, b, c; 5; 6). Nor apparently, have there occurred any delayed reactions beyond trigeminal neuropathy when freshly prepared solutions of the drug have been used (18).

During the war, when prepared solutions of stilbamidine were shipped to the Sudan, severe delayed reactions including fatalities were observed (18). These were promptly suspected to be the result of chemical change in the solution. Subsequent laboratory investigation revealed that, when exposed to light or ultra-violet rays, stilbamidine and other unsaturated diamidines were altered to produce toxic altho therapeutically inactive substances (19 to 21). With resumption of the method of preparing the solutions immediately before use no further difficulties were experienced. Pentamidine, being a saturated substance, is not subject to the photochemical change (18).

The symptoms of this delayed poisoning suggest either uremia or hepatic failure. In the only report found of histologic examination of tissues from human cases treated with stilbamidine Kirk and Henry (18) present observations on 4 liver sections obtained by viscerotome and of a scattering of organs in 6 cases that came to autopsy. All these cases were said to have been treated by bottled solutions of stilbamidine rather than freshly prepared solutions.

In only 6 of the 10 cases was death thought to be due to the drug. In only 2 of these 6 was kidney tissue available. In both the glomeruli were swollen and there was well marked degeneration of the tubular cells. In one, congestion seemed to resemble that in poisoned animals but a similar picture was seen in 2 cases not believed to have died of the drug. Necrosis was prominent in the liver of 7 cases. In one of these miliary tuberculosis was also present. In 5 central necrosis was noted and in 3 of these it extended into the midzone suggesting the appearance of acute or subacute yellow atrophy. Some degree of fatty degeneration was noted. Edema, congestion, leukocytic infiltration and proliferation of reticulo-endothelial cells was variable and was considered to be more probably related to the disease than the drug. No definite changes in the adrenals or heart muscle were noted. The spleens showed no change attributable to the drug. The authors conclude that the histologic findings were influenced by the disease or such extraneous factors as diet or intercurrent infection including infective hepatitis which was prevalent in the Sudan at that time. They feel that under suitable conditions the toxicity of the diamidines is negligible with doses that are therapeutically effective.

There are a number of reports of stilbamidine treated series without serious accidents (1a, 1b, 2, 3, 4, 5, 7, 8, 24). Individual doses of 100-150 mg. have been given to a total of over 5 Gm. The only delayed effect attributable to stilbamidine even when freshly prepared and less frequently to pentamidine has been a transient dissociated anaesthesia in the distribution of the trigeminal nerve (22). In a very recent communication which reports on the study of kidney and liver function in 16 myeloma patients before and after stilbamidine

therapy Arai and Snapper (23) conclude that "repeated injections of stilbamidine dissolved immediately before use have no delayed toxic effect on the liver. . . . The development of renal insufficiency in some myeloma patients during or following stilbamidine therapy is due to an exacerbation of pre-existing renal insufficiency caused by myeloma kidneys or by other pathologic change." They also failed to find any evidence of toxic effect on the hemopoietic system.

A recently noted morphologic effect of stilbamidine, reported by Snapper, is the appearance of basophilic cytoplasmic granules in the myeloma cells of certain cases of multiple myeloma. These have been shown to consist of ribose-nucleic acid and stilbamidine (7).

Because of the paucity of reports of post-mortem examinations in patients who have been treated with stilbamidine or pentamidine or both, it was decided to present here the cases of 3 patients treated with these drugs who came to autopsy. They were all suffering from multiple myeloma. These cases were included in the series presented by Dr. I. Snapper.

CASE REPORT

Case 1. History. J. M., male, aged 49, had a history of severe bone pain of 6 months' duration. X-ray examination showed multiple areas of rarefaction thruout the skeleton. Sternal marrow aspiration revealed 80-90 per cent myeloma cells. Bence-Jones protein was consistently present. Blood proteins were normal and calcium elevated. The patient was given 1.95 Gm. of stilbamidine in the course of one month resulting in marked relief of pain and tenderness. At the end of this period he became nauseated and began to vomit. The blood urea nitrogen rose and treatment for renal insufficiency was instituted. The urea nitrogen became stabilized between 24 and 26 mg. per cent and he subjectively improved. Stilbamidine was re-instituted and 2 more doses were given. The patient died suddenly 2 days after the last stilbamidine injection apparently in respiratory failure. He had received a total of 2.15 Gm. of stilbamidine. The basophilic stilbamidine ribonucleic acid inclusions were not found in the myeloma cells in this case.

Necropsy findings, summarized. Multiple myeloma involving vertebrae (with collapse of 12th dorsal), ribs, sternum and long bones. Myelomatous infiltration of liver and spleen (mild, diffuse). Obstructive renal tubular disease ("myeloma kidneys"). Atelectasis of lower lobe of right lung. Patchy congestion, hemorrhage and edema of lungs. Acute congestion of liver and spleen. Myeloid metaplasia of liver and spleen. Mild degenerative encephalopathy. Paget's disease of 4th lumbar vertebra and pelvic bones. Systemic and pulmonary arteriosclerosis (mild).

The kidneys weighed 500 Gm. together and presented a smooth surface, their architecture grossly seemed normal. Microscopically, however, they showed small cortical scars with focal atrophy of tubules. Mild tubular dilatation was irregularly present. The collecting tubules from the scarred areas contained dense, often lamellated, eosinophilic casts. Giant cells, macrophages and leukocytes surrounded some of the casts. There was spotty calcification of both distal convoluted and collecting tubules. A diffuse increase in interstitial tissue was present and a focal, lymphocytic infiltration was encountered. Glomerular capsules were frequently thickened. Little blood was present in the glomerular capillaries. Some of the interlobular arteries showed sclerosis but no arteriosclerosis was noted.

The liver showed congestion of sinusoids and edema of the Disse spaces. Many myeloma cells were present in the sinusoids as well as clusters of hematic elements.

The bone exhibited diffuse marrow replacement by myeloma cells and erosion of trabeculae and cortex. The parathyroid glands were of normal appearance.

Case 2. History. J. M., female, 47. In 1943 after an attack of pneumonia the patient

became progressively weaker and developed epistaxis and bleeding gums. On admission moderate enlargement of the liver and spleen were found. Marked anemia, thrombocytopenia, and a moderate leukopenia were present. The PSP test was only 30 per cent in 2 hours and the urine concentration did not go above 1,104 in 24 hours. Bence-Jones protein was present in the urine on some occasions. The total serum protein was consistently elevated (9 to 13 Gm.) most of it being globulin. The cephalin-cholesterol flocculation test varied from 0 to + + +, and the alkaline phosphatase was 12 King-Armstrong units. X-ray examination showed diffuse rarefaction in many bones. Sternal marrow examination disclosed large numbers of myeloma cells.

The patient was treated with repeated blood transfusions. Temperature fluctuated and rose to 103°F. There was profuse bleeding from the gums and pain in the chest and humeri.

She was given 150 mg. of stilbamidine every other day up to a total of 5.2 Gm. This was administered until a week before death. She improved symptomatically and objectively. However her marrow continued to consist almost entirely of myeloma cells. Many of these cells contained basophilic inclusions. (Snapper.)

After a month of an apparently improved state of health or comfort she lapsed into stupor, and bleeding of the gums and at the sites of needle punctures, as well as pain, recurred. Her condition steadily deteriorated and she died two months after admission.

Necropsy findings, summarized. Multiple myeloma with involvement of many bones, replacement of virtually all the marrow and much bone destruction. Anemia. Multiple ecchymoses, subcutaneous, retroperitoneal and intramuscular. Focal myelomatous infiltration of the liver. Myelomatous infiltration of lymph nodes. Hemosiderosis of the liver. Myeloid metaplasia in the spleen. Interstitial nephritis. Decubitus ulcers. Diffuse congestion, hemorrhage and edema of lower lobes of both lungs. Gastric distention. Congenital cyst of right frontal region of brain; multiple areas of gliosis and recent encephalomalacia.

The *liver* contained a grossly visible (3 mm.) myeloma cell nodule, as well as many microscopic foci. Iron pigment was abundant in the parenchymal and Kupfer cells. An occasional Kupfer cell contained fine eosinophilic granules. In many myeloma cells in the nodule mentioned basophilic inclusions could be made out under oil immersion.

The *kidneys* showed a diffuse interstitial lymphocytic infiltration. Occasional eosinophilic casts were noted. Atrophy of some tubules and hyalin-droplet degeneration, usually in the proximal convoluted tubule, were noted.

The *bone marrow* showed complete replacement of myeloid tissue by myeloma cells. Many of these contained the characteristic basophilic granules, some of which in clumps were seen also in histocytes (Snapper). A rare myeloma cell contained eosinophilic granules or droplets. The latter were sometimes larger than a red cell and of a hyalin character.

Case 3. History. G. E., male, 50 years of age, was a known diabetic for 24 years. In June 1945, he was first admitted with symptoms and X-ray findings interpreted as those of a duodenal ulcer. He was also found on admission to have hyperglycemia and glycosuria but he was anemic and had a history of leg pain of 6 weeks duration. He was discharged improved. In May of 1946 he returned in acute distress with severe pain and tenderness in the lower extremities, worse at night, and with hyperesthesia of the abdominal skin. Urinalysis was normal, aside from a 1+ albumin. Bence-Jones protein was absent from the urine. The formol-gel test was negative. Aspirated sternal marrow revealed typical myeloma cells. The blood chemical examinations were within normal limits. The thymol turbidity test was 2+. The red cell count was 2,850,000 with a color index of 1. and the white cell count was 3900 with 22 per cent eosinophiles. X-ray examination revealed compression fractures of D 10, 11, and 12 and compression of D 7, 8, and 9. Indefinite areas of increased density were noted in the humeri, femora and ischia and pubes. The patient was given 100 mg. of pentamidine daily for a total of 1300 mg. without appreciable change in his condition. He was then given stilbamidine daily for a total of 4.5 Gm. The patient experienced considerable lessening of pain and disappearance of hyperesthesia. He was discharged in August 1946 but readmitted 6 weeks later with complaints of weakness of 5

days duration and loss of weight and strength. Blood sugar was 380 mg. per cent and urine acetone 4+. Blood nitrogen was mildly increased. With treatment the glycosuria and acetoneuria cleared up but he developed a picture of shock with a low blood pressure and died 48 hours after admission in circulatory collapse. Stilbamidine ribonucleic acid inclusions were never found in marrow preparations in this case.

Necropsy findings, summarized. Multiple myeloma involving many bones with bone destruction. Compression of vertebrae. Myelomatous infiltration of spleen (mild). Renal arteriosclerosis and arteriolosclerosis. Atherosclerotic occlusion right coronary artery. Myocardial fibrosis, left ventricle. Pancreatic fibrosis and hyalinization of islets of Langerhans. (Diabetes mellitus, clinical.) Hemosiderosis of liver, marked, and of spleen. Cortical atrophy of cerebrum.

Microscopic studies revealed myeloma cells in the marrow of various bones in small nodules and scattered diffusely thru surviving hematopoietic tissue; with bone destruction and herniation of intervertebral discs.

The *pancreas* showed arterio- and arteriolosclerosis with hyalinization of islets which gave a weak reaction for amyloid.

The *liver cells* and an occasional Kupfer cell contained hemosiderin. The Disse spaces were irregularly distended.

The *kidneys* were affected by marked arterio- and arteriolosclerosis. Diffuse interstitial fibrosis with tubular atrophy, alternating with mild dilatation was noted. The interstitial tissue appeared edematous but contained almost no lymphocytes. A few intensely eosinophilic casts were present especially in collecting tubules. A few tubules were almost cystically dilated and filled with eosinophilic coagulum. The glomeruli showed mild diffuse intercapillary thickening with an occasional ill-defined eosinophilic mass. There was hyaline thickening of Bowman's capsule and frequent hyalinization of afferent arterioles.

A microscopic area of phlegmonous gastritis was noted.

DISCUSSION

In the 3 cases presented here no major morphological change attributable to the drug treatment was noted. The findings were not different from those in multiple myeloma cases not treated with stilbamidine. Changes found in the livers were referable to the anemia, circulatory failure, multiple transfusions, myelomatous infiltration, advanced cachectic condition, in short, the multiplicity of derangements that make up the myelomatous state. Renal changes in Case 1 were characteristically those of the so-called "myeloma kidney" and in Case 3 those of arteriolosclerosis in a diabetic of many years duration. In Case 2, they were less well-defined being those of a chronic degenerative type with a marked interstitial lymphocytic infiltration. They, too, are attributable to the advanced malignant state. Nor were major effects evident in other organs that appeared relevant to the use of a toxic substance or dissociable from the ravages of multiple myeloma, diabetes or aging.

In an effort to follow the one morphologic lead so far revealed in stilbamidine treated myeloma cases,—namely the basophilic inclusions repeatedly referred to above, a more particular scrutiny of the ribose nucleic acid of certain normal cells was undertaken. Sections of the pancreas as an organ abundantly supplied with ribose nucleic acid were stained with methyl green-pyronin and toluidine blue. The 3 cases reported here and sections from 4 other more recent stilbamidine treated cases, not described here were examined. 14 controls consisting of myeloma cases not treated by stilbamidine and a scattering of other non-mye-

loma cases were similarly studied. Unsatisfactory staining—attributable to poor fixation—made it necessary to exclude Case 1. But in cases 2 and 3, and 3 of the 4 other stilbamidine treated cases (thus 5 out of 6) tiny pyroninophilic round or oval granules were seen in the centro-acinous and duct cells of the pancreas. One or a number up to 6 or 8 of such granules were present in individual cells. The number of cells showing these granules varied from many in a single field in some cases to relatively few in other cases. Rarely, similar granules were present in islet cells. They were never seen in the ribose-nucleic acid rich acinar cells, although they stained with pyronin and with toluidine blue as does ribose nucleic acid. The cells in which they occurred did not appear otherwise altered. Aware now of their presence it was possible to discern them as hazy basophilic granules in Hematoxylin-eosin sections. These granules were not found in any of the control cases and were present in stilbamidine treated cases that did not show myeloma-cell inclusions, as well as several that did.

Sections of liver were also stained with methyl green-pyronin. In those from the 3 cases herein discussed and 2 other treated cases minute pyroninophilic granules were found in duct epithelial cells. These were present in large numbers in almost all duct cells.² In the 6 non-treated cases examined they were not seen.

At present no more can be said concerning these findings. The examination of the kidneys and the other organs through which stilbamidine might be excreted has not been completed at this reporting.

CONCLUSION

Three cases of multiple myeloma treated by stilbamidine showed no apparent tissue damage attributable to the drug. In one case the stilbamidine ribose nucleic acid granules in myeloma cells described in marrow smears by Snapper were demonstrated. In 2 of these cases and 3 of 4 other stilbamidine treated cases small pyroninophilic granules were demonstrated in the centro-acinous and duct cells of the pancreas. All 3 and 2 other treated cases showed similar minute pyroninophilic granules in the duct cells of the liver. The granules were not found in the controls.

Since the above was written, Seager and Castelnovo (24) have reported on the effects of very large doses of stilbamidin (75–100 mg. per kg.) given in divided doses to rabbits and mice. Rabbits which survived for some time showed increased fibrous tissue in the liver and large, dense masses of histiocytes and fibroblasts around the periphery of hepatic lobules, in some cases occupying a large part of the lobule itself. Foci of necrosis of central hepatic cells were some times noted. Marked changes were noted also in the renal tubular epithelium.

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² The observations of pyroninophilic granules within liver cells will be discussed in other reports.

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INSULIN RESISTANCE

CASE REPORT

KERMIT E. OSSERMAN, M.D. AND HERBERT POLLACK, M.D.

The unusual insulin requirements in a diabetic is the object of the following case report.

History. The patient, a white male, aged 12½ years, was admitted to The Mount Sinai Hospital in February, 1947. The chief complaints, which had their onset three weeks prior to admission, were loss of weight, extreme thirst and frequent urination. Only on the day before admission was glycosuria discovered.

The boy had had chicken pox, measles and mumps. The tonsils and adenoids had been removed at the age of five years. Allergic rhinitis developed at the age of ten. Ragweed, plantain and dust gave positive skin reactions. His family history was positive for diabetes mellitus.

Examination. Physical examination on admission revealed a well developed boy, weighing 85 pounds. Except for a granular pharyngitis and deviated nasal septum, there were no other positive physical findings. His blood pressure was 110 mm. Hg systolic and 72 mm. Hg diastolic.

Laboratory data. Urine: colorless; 4 plus reaction to Benedict's reagent; acetone, 3 plus. Blood sugar was 460 mg. per cent; cholesterol, 340 mg. per cent; hemoglobin, 84 per cent (Sahli). The white blood count was 10,000 with 79 per cent polymorphonuclears of which 8 per cent were non-segmented.

Course. Crystalline zinc insulin was administered in divided doses of 10 to 20 units per hour, until the patient was brought out of ketosis. A diet of 2400 calories was prescribed, consisting of 270 grams of carbohydrate, 110 grams of protein and 100 grams of fat. It was found that 44 units of crystalline zinc insulin completely controlled the glycosuria. After a few days, crystalline zinc insulin was in part replaced by protamine zinc insulin. At the end of two weeks, the patient was discharged from the hospital. The diet was as described above. He was advised to inject 24 units of crystalline zinc insulin and 12 units of protamine zinc insulin, mixed in the same syringe, before breakfast daily. His fasting blood sugar was 100 mg. per cent. The fractional urines contained no glucose. He was discharged on March 15, 1947, weighing 90¾ pounds.

A few weeks later, the patient returned to school and to his usual activities. The fasting blood sugars were repeatedly found to be between 100 mg. and 150 mg. per cent, and his body weight increased to 95 pounds.

In April 1947 an incision was made into the gum for an impacted tooth. Concurrently the patient developed an upper respiratory infection with fever. His combined insulin requirements increased to about 60 units per day. Following the return of temperature to normal and resumption of normal activity, his insulin requirement remained at about 60 units per day.

In June, the patient developed acetonuria and glycosuria with loss of body weight, from 95 pounds to 88 pounds. Because the patient had an old history of sensitivity to allergens, an intradermal test was done and he was found to be positive to grass antigen. It was thought that the increasing requirements for insulin might be due to the allergic disturbance. Intradermal tests, with regular and protamine zinc insulin, gave positive skin reactions. At this time the insulin requirement had reached from 90 to 100 units of insulin mixture per day. The patient was desensitized to protamine zinc insulin by means of multiple (hourly) injections of small doses. His total daily requirement was divided into twelve doses given one hour apart the first day. The second day the total amount was given in six injections, two hours apart. The third day, the total insulin was divided into

four doses. The fifth day he was given a maintenance dose of 100 units of protamine zinc insulin before breakfast. However, this did not control the glycosuria, which occurred after breakfast, and he was given an additional injection varying from 15 to 25 units of crystalline zinc insulin before breakfast. His diet was changed to conform to a protamine regime, i.e., 200 grams of carbohydrate, one-fifth of the carbohydrate at breakfast; two-fifths at luncheon; and two-fifths at supper, with a night feeding of milk and crackers. The patient and his family were leaving for a hotel for the summer, therefore, strict regulations on protein and fat were lifted.

During June, July and early August, while the boy was away, he manifested occasional and transient acetonuria. The administration of 25 to 35 units of crystalline zinc insulin would eliminate this complication. However, in the latter part of August, upon return to New York City, he had increasing episodes of severe glycosuria and acetonuria. The insulin requirements had increased to 140 units of protamine zinc insulin and 110 units of crystalline zinc, each being given separately. His body weight now was 97½ pounds, height 59¼ inches. Erythrocyte sedimentation rate was 3 mm. (Westergren). At this point he started to lose weight. It was decided to hospitalize him again to study his insulin resistance.

The patient was re-admitted to The Mount Sinai Hospital on August 26, 1947. His weight was 94¾ pounds; temperature, 100.2°F.; pulse, 92; and respirations, 18 per minute. There was no evidence of insulin atrophy or hypertrophy. The temperature returned to normal after four days, and remained so throughout his stay. On September 9th, the day of discharge, the body weight was 98 pounds.

While in the hospital the patient was subjected to a number of laboratory tests. The blood study showed: hemoglobin, 13.6 Gm.; white blood count, 6,600 with a normal differential (except for 5 per cent eosinophiles). Upon repetition of the differential count, the eosinophilia decreased to 2 per cent. The erythrocyte sedimentation time was 7 mm. (Westergren) in an hour. Liver function tests showed 1.7 Gm. of hippuric acid in 100 cc., and bromsulphaline test revealed less than 1 per cent retention after 45 minutes (5 mg. test), which are normal. Agglutination tests for typhus, paratyphoid A and B, brucellosis trichinosis, and infectious mononucleosis were done. All tests were negative except typhoid that was positive in a dilution of 1 to 40 (patient had previously been immunized for typhoid). Intradermal trichinella skin test was negative.

X-ray examination. Intravenous urogram showed questionable dilatation of the left kidney pelvis and calices. Spina bifida of the upper sacral segment was present. The chest showed no abnormality in the lungs or heart. The skull and sella turcica were normal.

Electrocardiography revealed a regular sinus rhythm with a P-R interval of 0.12 seconds, a slight tendency to right axis deviation. There was no evidence of myocardial damage.

Examination of the nose and throat disclosed follicular lymphatic hyperplasia of the posterior pharynx, as seen in allergic states. Nasal septum was deviated to the left with large spur. Nasal mucosa was pale and boggy, as seen in allergic rhinitis. Nasopharynx, larynx, and ears were normal. X-ray study of the sinuses revealed slight haziness on the floor of the right antrum. No intervention during the ragweed season was planned.

Quantitative Ascheim-Zondek test showed no increase of pituitary secretion. Seventeen keto-steroid excretion was 3 mg., which is low. Insulin antibodies in the blood were not found to be increased. Basal metabolic rate was minus 19 per cent.

During his stay in the hospital, the patient was completely regulated, without glycosuria or shock, with 200 units of protamine zinc insulin and 25 units of crystalline zinc insulin. His diet was increased to 200 grams of carbohydrate; 120 grams of protein; and 200 grams of fat. Carbohydrate was divided into portions of one-fifth at breakfast, two-fifths at luncheon, and two-fifths at supper. The proteins were also divided into portions of one-sixth, one-third and one-half, for the above three meals. No fruit was permitted at breakfast. A night meal of milk and crackers was given. He was discharged on September 9th to follow this regime.

Upon returning home, the patient developed glycosuria before breakfast. The insulin dosage was changed to 220 units of protamine zinc and 40 units of crystalline zinc insulin

given in separate syringes in the morning before eating. On this regime the glycosuria was temporarily controlled. However, within the week he was again having glycosuria with occasional acetonuria.

In October, the patient was examined by Drs. Joslin and Root in Boston. They have confirmed the previous findings. They reported that they could find no cause for the increased insulin requirements and found no need for a major change in diet. He was receiving 140 units of protamine zinc insulin and 150 units of crystalline zinc insulin in separate syringes before breakfast daily. A concentrated insulin containing 500 units in each cc. was used in order to reduce the volume.

The patient returned to New York. The insulin requirement continued to rise. By November his requirements reached between 400 and 500 units of insulin per day. This was taken in the form of 240 to 260 units of protamine zinc insulin, and the remainder crystalline zinc. However, his weight was 99½ pounds, height 60¼ inches in stocking feet, and general condition was excellent. A 24 hour urine specimen contained traces of insulin.

In the latter part of November, testosterone propionate, in doses of 5 mg., was injected bi-weekly in an attempt to suppress pituitary excretion and thereby possibly lower the insulin requirement. This was continued for four weeks without any effect on the insulin requirement. Therefore, testosterone propionate therapy was discontinued. During the latter part of December and early January his basic requirements were 280 units of protamine zinc insulin plus 250 units of crystalline zinc insulin, taken in separate syringes before breakfast. In addition, on days when he showed acetonuria, an additional 50 to 75 units of crystalline zinc insulin was prescribed. On February 2nd, the patient experienced shocks all morning; all specimens of urine were free from glucose. The insulin dosage was lowered to 100 units of protamine zinc insulin plus 125 units of crystalline zinc insulin. After three days of this lower dose, he again required an increase to 240 units of protamine zinc insulin and 150 units of crystalline zinc insulin. On this latter dose he had neither glycosuria nor hypoglycemia. During the next four months his insulin requirement varied between 400 and 500 units per day. In June 1948, hypoglycemic episodes recurred and the insulin dosages were lowered rapidly to between 125 and 150 units per day.

At present (October 1, 1948) he is using 120 units of protamine zinc insulin plus 20 to 30 units of crystalline zinc insulin, taken in separate syringes before breakfast. His dietary intake is approximately 3000 calories per day. His weight is 106 pounds, and height 62¾ inches. His fasting blood sugar is 148 mg. per cent. Urine contains no glucose. Blood pressure is 90 mm. Hg systolic, and 60 mm. Hg diastolic. His ocular fundi are normal.

Comment. There are several significant points in the foregoing case history. The remarkable fluctuation in insulin requirements did not prevent this boy from gaining 21 pounds in body weight and growing almost 4 inches. The approximation of normal development indicates, that, when adequate diet is prescribed, and the proper amount of insulin is administered, metabolic processes may be kept close to normal. This shows that the proper amount of insulin is that amount required to control the symptoms, be it 5 units or 500 units.

The fate of this insulin could not be determined. The urinary assay disclosed only traces of insulin in the twenty-four hour samples, so that it may be assumed that most of it was destroyed or inactivated.

GIANT OVARIAN CYST IN A TWENTY YEAR OLD GIRL

CASE REPORT¹

ROBERT A. HERFORT, M.D.

The surgical journals of forty years ago are replete with clinical records of cystic ovarian tumors weighing fifty pounds or more (1, 2, 3, 4). Bullitt (1) in 1900 reported a series of 25 ovarian tumors, all weighing over 100 pounds, including a 245 pound specimen. However, large ovarian cysts are rarely encountered now, probably because of earlier diagnosis and timely surgical intervention. Such cysts may present difficulties in diagnosis when they occur in the young adult, as shown by the following case.

CASE REPORT

History (Adm. #583197). M. G. R., a twenty year old white woman, a college student, was admitted on July 11, 1948, complaining of progressive abdominal enlargement in the course of the previous two years. The onset of the enlargement was painless and became apparent only when her clothes became tight about her waist. No other symptoms were present at that time and medical advice was not sought until one year had elapsed. The patient was examined by several physicians and was told that the abdominal swelling was due either to fat deposition or gaseous distention. One physician suggested the presence of an abdominal cyst. She gained approximately 25 pounds during this two year period. For the ten months preceding her admission to the hospital she noted wasting of her face and extremities concomitant with progressive, painless enlargement of the abdomen. Moderate asthenia and dyspnea on exertion were noticed during the six months before entering the hospital. She had no symptoms referable to the gastrointestinal tract and there were no urinary complaints except for minimal frequency of two months' duration. Her menses were normal. The past and familial histories were non-contributory.

Examination. The patient was a thin young woman, appearing chronically ill, displaying a marked protuberance of the abdomen and an emaciated thorax. She weighed 142½ pounds. The lungs were clear. The only significant cardiac finding was the point of maximum intensity being in the fourth interspace on the mid-clavicular line. The blood pressure was 110 systolic and 80 diastolic. The abdomen was diffusely but not tensely distended with some symmetrical bulging in the flanks. A markedly fluctuant fluid wave was elicited over the entire abdomen extending into the flanks with dullness to percussion over the same area. No masses or viscera were palpable; there was no tenderness. Pelvic examination was not done because of an intact hymen. Rectal examination was negative. All four extremities were thin; the lower extremities were not edematous.

Laboratory data. Blood: hemoglobin, 13.8 gm.; white cell count, 6100 with a normal differential. The urine was negative.

X-ray examination of the chest revealed marked uniform elevation of the anterior portion of the diaphragm with elevation of the heart and mediastinum. Fluoroscopy demonstrated limitation of movement of the diaphragmatic domes ascribable to increased intra-abdominal pressure. A gastro-intestinal study revealed no intrinsic defect in stomach, small intestines, or colon. Gross distortion and displacement of the stomach were noted with this viscus being rotated anteriorly so that the greater curvature lay against the left dome of the diaphragm. The entire length of small intestines and the right colon were displaced to the right with the distal colon crowded into the left flank (fig. 1). A smooth radiolucent mass occupied the central area of the upper and mid-abdomen extending under the costal margins.

¹ From the Surgical Service of Dr. John Garlock, The Mount Sinai Hospital, New York.



FIG. 1. Preoperative film of abdomen 6 hours after barium meal

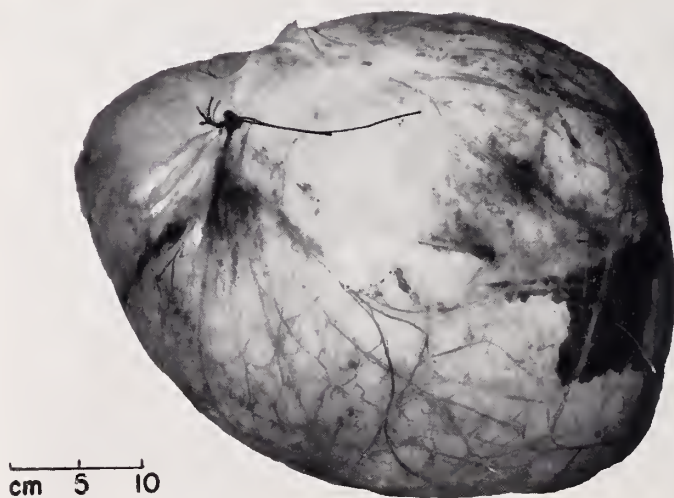


FIG. 2. Serous cystadenoma removed at operation. Specimen refilled after removal

Course. A eyst, pancreatic or mesenteric in origin, was considered as the most likely diagnosis, but the surgeon's preoperative diagnosis was ovarian eyst. Accordingly, an exploratory laparotomy through a long right rectus incision was carried out on her second hospital day.

A watermelon sized, flaccid smooth walled cyst was found filling the abdominal cavity from the pelvis to the phrenic domes. The cyst was partially evacuated by aspirating trochar and delivered onto the abdominal wall. It was found to be quite free but for attachment by a broad pedicle to the right adnexa. The uterus and left adnexa were normal. There was no ascites. The entire length of small bowel was found in the right lumbar gutter. A right salpingophorectomy was performed and the abdomen closed. The patient withstood the operative procedure well.

The cyst contained fifteen liters of a colorless opalescent fluid, the specific gravity of which was 1.010 with a protein content of 94 mg per cent. The pathologists reported the cyst to be a benign unilocular cystadenoma (fig. 2).

The patient's convalescence was satisfactory, the wound healing uneventfully. She was discharged on the eighth postoperative day weighing 105 pounds or $37\frac{1}{2}$ pounds less than on the day of admission. One month later when reexamined she was found free of complaints and the operative wound was well healed.

DISCUSSION

The dominant feature in this case is the occurrence of a growing abdominal tumor in a young adult, which escaped recognition by several physicians so that surgical intervention was delayed for over $1\frac{1}{2}$ years. Indeed, the diagnosis of a massive ovarian tumor in a young adult is obviously difficult at times due to its relative infrequency and to the inevitable confusion with other intra-abdominal tumors. Barzilai (5) states that ovarian serous cystadenomata (endosalpingiomas of the ovary in Barzilai's histogenetic classification) have been reported in all age groups from puberty to senility. Ewing (6) points out that the decursus morbi of the serous cystadenoma in particular is slow and benign requiring four to fifteen years to attain large dimensions. The gigantic cysts of the older literature were reported in women in the fourth and fifth decades of life (1, 2).

Large ovarian cysts must be differentiated from a number of conditions leading to abdominal enlargement such as obesity, ascites, tympanites, urinary bladder distention, hydronephrosis, pancreatic cysts, omental and mesenteric cysts, encysted tuberculous peritonitis, hepatic and splenic tumors, uterine neoplasms, hydrosalpinx, tubal and uterine gestations. A definite diagnosis, as several authors (7, 8) have pointed out, frequently can only be made at laparotomy.

Early surgical intervention is indicated to determine whether the histological character is benign or malignant (7, 8). Moreover, the danger of rupture of the neoplastic cyst as well as that of torsion with hemorrhagic infarction is omnipresent and can be obviated only by early removal.

In the case reported, note should be made of the relative absence of pressure symptoms despite the manifest distortion of the gastrointestinal tract and the gross upward displacement of the thoracic viscera. The benign insidious growth of the cyst with consequent physiologic adjustment of contiguous systems probably accounted for the patient's comfort for two years.

SUMMARY

A case report of a 37 pound serous cystadenoma of the ovary which was removed from a twenty year old girl, is presented.

The difficulties encountered in diagnosis of large ovarian cysts are emphasized.

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NUCLEIC ACID DEPOLYMERIZATION IN SYSTEMIC LUPUS ERYTHEMATOSUS* **

P. KLEMPERER, M.D., B. GUEFT, M.D., AND S. LEE, M.D.

Gross, (1), in 1932, reported the presence of "clumps and packets of hematoxylin staining bodies" in cardiac vegetations of Libman-Sacks disease, subsequently identified with acute lupus erythematosus. He believed that these bodies originated from nuclear material and considered them pathognomonic. In 1940, Ginzler and Fox (2) found hematoxylin-staining masses in necrotic lymph nodes of a case of lupus erythematosus. These authors also found basophilic particles within the loops of renal glomeruli. Klemperer, Pollack and Baehr (3) in 1941 observed identical material in the focal glomerular loop necrosis which they found present in 17 of 20 cases.

Within the last year we have observed three cases of acute lupus erythematosus in which we found the same hematoxylin-stained bodies. These were localized not only in the heart, lymph nodes and kidneys, but also in sections from various widely dispersed sites, always in tissues of mesenchymal origin. These changes were so striking that we were led to reexamine our lupus material. We studied 34 cases which had been unequivocally diagnosed, both clinically and anatomically. In 31 of these cases, identical "hematoxylin-stained" bodies were found in one or more sites. In 19 of the 34, the bodies were present in two or more loci, indicating generalization of the process. In several cases this generalization was most striking.

Kidneys and endocardium were, in our series, affected most commonly. For this reason these organs were utilized in the study of controls. Neither in a large quantity of random material, nor in selected cases of rheumatic or bacterial endocarditis, diffuse and focal glomerulonephritis, malignant nephrosclerosis or periarteritis nodosa were similar bodies observed.

These bodies, wherever found, assume a strikingly similar appearance. In hematoxylin-eosin preparations they are reddish-purple. They are homogeneous, without internal structure. They vary in size from that of a cell fragment to almost macroscopic proportions. Their origin from nuclei can easily be traced. Fibroblasts, endothelial cells, lymphocytes, polymorphonuclear leucocytes and histiocytes if affected show a striking change of the chromatin, viz. homogenization and purplish-red staining as seen in the free hematoxylin bodies. In our material, no cells of other than mesenchymal origin have been implicated. Our material has been limited to histologic sections; others (Hargraves, Haserick, et al.) (4) have observed peculiar nuclear alterations in the aspirated bone marrow of cases of acute lupus erythematosus, which they feel are specific. Our studies indicate identity in the nature of the phagocytized material of their "L.E." cells with the small hematoxylin-stained bodies.

* From the Department of Pathology, The Mount Sinai Hospital, New York City.

** Read at the annual meeting of the Am. Ass. of Pathologists and Bacteriologists, April 15, 1949.

Histochemical analysis of these bodies would have been impossible without the guidance and assistance of Dr. A. W. Pollister and Mrs. C. Leuchtenberger, the Department of Zoology, Columbia University, New York. Spectrophotometry in the ultraviolet shows a very strong absorption at a wavelength of 2537 Å. This establishes the bodies as containing nucleic acid. Digestion with ribonuclease fails to affect the bodies. Furthermore, the Feulgen reaction is positive. This constitutes convincing evidence that the hematoxylin-stained bodies are derived from nuclear chromatin (desoxyribose nucleic acid). However, they stain only weakly with methyl green, and take a strong pyronin stain with the Unna-Pap-penheim mixture. Kurnick (5) has shown that if desoxyribose nucleic acid be depolymerized *in vitro*, it loses its affinity for methyl green and becomes pyroninophilic, without losing Feulgen positivity. (Pollister and Leuchtenberger have recently demonstrated the same in cytochemical investigations (6).) Our findings thus indicate that the desoxyribose nucleic acid in the hematoxylin-stained bodies is in a depolymerized state.

It then becomes apparent that one of the factors in acute lupus erythematosus is a disturbance of the nucleic acid metabolism of the cells of the mesenchyme manifesting itself in depolymerization of the desoxyribose nucleic acid.

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Acute Appendicitis Occurring During the Course of Other Diseases. E. S. HURWITT. New England J. Med., 236: 20, January, 1947.

Ten representative cases of acute appendicitis occurring in the course of other diseases are presented. The tendency to interpret such cases as possible manifestations of the underlying disease rather than as an independent intraperitoneal lesion is pointed out. The consequences of a temporizing attitude in terms of the increased morbidity of appendiceal peritonitis is discussed. It is emphasized that acute appendicitis must be diagnosed on the clinical evidence (symptoms and signs) regardless of any coexisting disease.

A Psychiatric Treatment Program in Combat. M. KAUFMAN AND L. E. BEATON. Bull. Menninger Clin., 11: 1, January, 1947.

This is a report on the functioning of a previously planned treatment program for psychiatric patients in combat in the Okinawa campaign. The basic concepts and the organization of the treatment program are presented together with details of the type of treatment at various echelons. At the field hospital level the emphasis was primarily on individual psychotherapy, i.e., reassurance, emotional catharsis and especially the use of hypnosis rather than chemotherapy for sedation and catharsis; rest, group psychotherapy, recreational activity, ward organization and a work program. The incidence of neuropsychiatric cases and some of the precipitating factors are discussed. 80-90 per cent of these cases were returned to effective divisional duty.

Spontaneous Cyst of the Iris. J. LAVAL. Am. J. Ophth., 30: 55, January, 1947.

A 57 year old white male had a large, pale brown, cystic mass involving the temporal half of the iris of the left eye. Vision in this eye was reduced to finger counting but the tension remained normal. On enucleation it was found that the cyst involved half of the iris and had replaced its usual stroma. The filtration angle in this area was missing but the tension withal had not been elevated clinically. These spontaneous cysts of the iris without any history of trauma or prior inflammation are not common, only 41 cases having been reported up to now. They are usually found in patients under 20 years of age but one other case had been reported in a 58 year old male. There is no consensus of opinion as to whether the cyst is mesodermal or ectodermal in origin but the fluid of the cyst is secreted by the epithelial cells which line the cyst cavity. The various standard textbooks of ocular pathology have no illustrations of a case similar to the one here reported.

Treatment of Early Syphilis with Penicillin. T. H. STERNBERG AND W. LEIFER. J. A. M. A., 133: 1, January, 1947.

Analysis was made of the records of 1,400 soldiers treated for early syphilis with 60 injections of 40,000 units of penicillin at three hour intervals for seven and one-half days. About 84 per cent of patients were observed for nine months or longer. The observed failure rates

were 5.7 per cent in 600 seronegative primary cases; 10.1 per cent in 507 seropositive primary cases; and 17 per cent in 263 secondary cases. Abnormal spinal fluid after treatment was noted in 0.69 per cent of over 700 patients examined, and there was no symptomatic neurosyphilis. It was suggested that the 15 per cent failure rate in Negroes, as contrasted with the 5 per cent rate in whites, was due to a higher incidence of reinfection, since the rate of all venereal disease was consistently greater in this racial group.

A Case of Gargoylism. L. STRAUSS. New York State J. Med., 47: 157, January, 1947.

The gross and microscopic findings in a case of gargoylism are briefly reported. There were severe skeletal deformities including scaphocephaly, dorso-lumbar kyphosis, broadening of ribs, shortening and curving of long bones; corneal clouding, hydrocephalus, gargoyle facies; cardiac enlargement with thickening of the valves; intimal plaques in the aorta and other arteries; enlargement of the liver and spleen. Microscopically, large vacuolated cells were found in many organs and tissues, indicating storage of an unidentified substance in the reticulo-endothelial system, and in the parenchymatous as well as mesenchymatous structures. The central nervous system showed changes similar to those found in amaurotic family idiocy. The condition is genetically determined.

The Role of Traumatism in the Induction of Initial Pneumothorax: Further Studies. I. G. TCHERTKOFF AND I. J. SELIKOFF. Quart. Bull. Sea View Hosp., 9: 1 January, 1947.

It had previously been shown that induction of pneumothorax with sharp needles will always result in injury to the lung during the initial pneumothorax. It has been claimed that this will not occur if dull needles are used. In 10 patients, pneumothorax was induced with a dull needle and only small amounts of air introduced. In each case, a pneumothorax space was found larger than could be accounted for by the amount of air put in. In 19 patients, only pleural readings were taken and the blunt needle then withdrawn without giving any air. In each of these patients, a pneumothorax space was found, occasionally very large. Every initial pneumothorax is first a traumatic pneumothorax and this is true whether a sharp or a dull needle is used for the induction. The needle, inserted through the parietal pleura, injures the visceral pleura and air escapes from the traumatized lung. This is the real initial pneumothorax. The manometer readings we observe are those of this traumatically-produced pneumothorax and it is into this space that we introduce air from our pneumothorax apparatus.

Tuberculous Dactylitis in the Adult. A. L. UMANSKY, P. T. SCHLESINGER AND B. B. GREENBERG. Arch. Surg., 54: 67, January, 1947.

Tuberculous dactylitis or spina ventosa in the adult is rather rare. The literature discloses only isolated reports from many foreign countries. The authors describe a case of a 19 year old male, who, shortly after the development of a right tuberculous hydropneumothorax, complained of swelling and pain of the proximal phalanx of the left index finger. Serial roentgenograms over a period of 2 years revealed progressive destruction of the involved proximal phalanx associated with increased soft tissue swelling and the final development of a pathological fracture. Resection of the involved finger including the metacarpal head and neck was followed by an uneventful recovery. The pathologic diagnosis was tuberculous osteomyelitis. This lesion was differentiated from that seen in childhood as well as from those seen in syphilis, Boeck's sarcoid, coccidioidmycosis, leprosy and yaws.

New Modification of the McReynolds Transplantation for Pterygium. J. GOLDSMITH. Arch. Ophthalm., 37: 194, February, 1947.

This paper offers an explanation for the recurrence of pterygiums and presents a new modification of the McReynolds operation for their prevention. This new procedure has been employed in over 300 cases with satisfying results. In the original McReynolds transplant, the suture which was passed blindly through the loose subconjunctiva, frequently failed to engage the denser episcleral tissue resulting in poor scar formation and eventually

leading to retraction of the pterygium. The new method in which the conjunctiva and Tenon's capsule is incised, enables the surgeon to take broad episcleral bites under direct observation, thus assuring the formation of firm adhesions. Chronic catgut is substituted for black silk. A traction suture for broad and large pterygia is also described.

Incidence of Acute Coronary Artery Occlusion. A. M. MASTER. *Am. Heart J.*, 33: 135, February, 1947.

If the mortality rate of acute coronary occlusion is accepted as 15 per cent, about 800,000 attacks of acute coronary occlusion occur yearly. One man in 40 and 1 woman in 115 experience an attack of acute coronary occlusion annually. The increase in diseases of the coronary arteries is explained by the increased span of life brought about by reduction in infectious disease of childhood and adult life, advances in medical knowledge, and improvement in public health and sanitation. Physicians are not more prone to acute coronary occlusion than are other persons. It should no longer be thought of as the "doctor's disease."

Carcinoma Simulating Pulmonary Tuberculosis. L. E. SILTZBACH. *Am. Rev. Tuberc.*, 55: 170, February, 1947.

Industrial mass surveys which include many persons above 40 years of age are bringing to light silent circumscribed lung carcinomata. Two patients with such neoplasms, the shadows of which were first disclosed in survey films, were treated for pulmonary tuberculosis 7 and 16 months, respectively, before the nature of the lesion was recognized. The differential diagnosis between a solitary noncavitary tuberculous focus and a slow-growing circumscribed carcinoma in patients over 40 years of age particularly when the lesion is situated in the upper lobes is discussed. The roentgenographic characteristics of such neoplastic and tuberculous lesions are presented. Early exploratory thoracotomy is suggested when the diagnosis is equivocal, since this procedure may be life-saving if the lesion is carcinoma.

Etiologic Evaluation of Asthma in 100 Cases Returned from Overseas. A. P. FISHMAN. *J. Allergy*, 18: 115, March, 1947.

At a military port of debarkation, it was noted that a disproportionately high number of patients were evacuated to the United States with the diagnosis of asthma. Investigation of specific etiologic factors was undertaken. In a large group of evacuees, it was demonstrated that emotional stimuli as well as specific antigens are capable of initiating and perpetuating attacks of asthma in susceptible individuals. Stress is placed upon the recognition of psychogenic factors and the relief which can be obtained from psychiatric therapy. Illustrative case histories are included.

A Comparative Study of Pathogenicity and Antigenicity of Four Strains of Herpes Simplex.

A. L. FLORMAN AND F. W. TRADER. *J. Immunol.*, 55: 263, March, 1947.

Comparative studies of pathogenicity and antigenicity were made of four strains of *herpes simplex* in order to investigate some of the differences which may exist between strains of a single viral species. Mice, rabbits, guinea pigs, white rats, hamsters, cotton rats and chick embryos were observed after inoculation of mouse brain emulsions by various routes. Although *herpes simplex* is a pantropic virus, differences between strains are accentuated by certain tests. Thus, death of the majority of animals following corneal infection of the rabbit or intranasal inoculation of the cotton rat can be used to indicate strains with prominent neutrotropic tendencies, while marked local reactions after intradermal injection of the guinea pig are indicative of dermatotropism. These distinctions probably hold only for the particular species of animals and routes tested, as the strain which was most dermatotropic in our laboratory, "O", was the cause of fatal encephalitis in a human being. It is not known whether these differences in potentiality of herpes strains are of epidemiologic significance. The development of neutralizing antibodies in rabbits after corneal and intra-abdominal inoculations was studied. Significant levels of antibody

were present by 3 weeks and peak titers were attained by 6 weeks. The serologic relationships were investigated by testing the corneal reactivity of immunized rabbits to homologous and heterologous strains and by cross neutralization tests in mice and chick embryos. The chick embryo tests were found to be the most sensitive and satisfactory for this purpose.

Absorption of Penicillin from the Vagina. M. A. GOLDBERGER, R. I. WALTER AND L. LAPID. *Am. J. Obst. & Gynec.*, 53: 529, March, 1947.

Ten women with no lower genital tract pathology were selected for this study. Five suppositories, each containing 100,000 units of penicillin in a cocoa butter base, were placed in the vagina. The total urinary excretion of penicillin in the urine for twenty-four hours varied between 33,425 units and 142,000 units, the average being 91,957 units. The average blood penicillin level was 0.38 units per cc. of serum at the end of thirty minutes; 1.35 units per cc. at the end of one hour; 0.96 units per cc. at the end of two hours; and 0.38 units per cc. at the end of three hours. It was evident that penicillin was readily absorbed through the vagina and therapeutic blood levels were easily obtained and maintained for at least three hours. It was suggested that this method warrants clinical trial.

"Ill Health" as an Expression of Anxiety in a Combat Unit. M. R. KAUFMAN. *Psychosomatic Med.*, 9: 104, March, 1947.

An anonymous questionnaire among a combat division undergoing rest and physical rehabilitation after a campaign showed only 7 per cent who felt they were in good health. This was related to the presence of many psychosomatic manifestations of anxiety (sleeplessness, moist, clammy hands, upset stomach, etc.). Under combat conditions soldiers in this division had been returned to duty with little or no treatment. In another combat division neuropsychiatric casualties had been treated or evacuated. In this second division 18 per cent felt they were in good health, a significant difference. Individuals may present the psychosomatic manifestations of anxiety and neurotic tension as complaints of "ill health". This has implications for civilian practice.

Acute Coronary Insufficiency. A New Concept of Acute Coronary Diseases. A. M. MASTER AND O. AUERBACK. *U. S. Nav. M. Bull.*, 47: 226 March, 1947.

Acute coronary artery diseases alone, with the possible exception of cancer, cause more fatalities than any other disease. Its importance is therefore manifest. The concept of acute coronary insufficiency as a complete clinical entity, that is possessing definite etiological factors, pathologic pattern, physiological mechanism, electrocardiographic type, and preventive and curative treatment, is new. The treatment is prophylactic, preventive, and frequently specific and curative. The second form of acute coronary disease is acute coronary occlusion. This is a sudden complete closure of the vessel. The treatment of this disease, thus far, is symptomatic and for the prevention of complications.

Suggested Methods for the Control of the Present Epidemic of Tinea of the Scalp. S. M. PECK. *Pennsylvania M. J.*, 50: 569, March, 1947.

Scalp ringworm has reached epidemic proportions in recent years. The type of fungus mainly responsible is the *M. audouini*. However, the *M. lanosum* was also found as an etiologic agent. The experiences of the author in the nationwide epidemic while he was investigating this for the Public Health Service is given. Methods of diagnosis are discussed. Various topical treatments which have been successful in obviating the use of x-ray epilation, in many instances are given in detail. There is given a plan of treatment and epidemic control which is in part proposed by the United States Public Health Service with a number of modifications by the author.

Learning the Lempert Fenestration Operation. S. ROSEN. *Arch. Otolaryng.*, 45: 335, March, 1947.

The fenestration operation for deafness is probably the most difficult one in sur-

gery today. In no other operation are slight errors in technic apt to be as costly. Learning to do this new and complex operation involves not only learning new manoeuvres but also dropping out the old established manoeuvres of temporal bone surgery performed for many years. The student learning this procedure must watch expert technique in the operating room and then try to imitate this technique on the cadaver. This method of watching and doing must be repeated again and again until the operation can be performed faultlessly many times on the cadaver. The author believes that perfection cannot be achieved until 100 cadaver operations are done and a similar number observed in the operating room. The reason for persisting in sustained cadaver work is that it is thus that one learns to control technical errors. We achieve this control by committing on the cadaver the very errors which make the operation dangerous. When we learn how the dangers occur, we learn then what "not to do." If the surgeon learning fenestration technic has not erred repeatedly on the cadaver, he will tend to be too tense in the operating room, because he is anticipating those dangers which he has learned to fear and dread but which he has not been able to "get out of his system" by constant and familiar practice. Cadaver practice should supplement early operational experience until a good backlog of successful performances has been achieved.

Response of the Heidenhain Pouch to Repeated Application of Eugenol. H. A. SOBER, B. P. SONNENBLICK AND F. HOLLANDER. *Federation Proc.*, 6:292, March, 1947.

Eugenol emulsion was allowed to remain in a dog's pouch for 15 minutes. Thereafter, 4 successive 30-minute specimens of mucus secretion were collected. This stimulation and collection was repeated 6-7 times. Follow-up experiments of shorter duration were performed after 36 hours and 3-5 months. Physical, chemical and microscopic studies of all specimens were done. Striking changes occurred during the early cycles. At first the mucosa secreted opaque, jelly-like mucus. Thereafter, decrease of mucus output, and dilution with serous material were noted. The later specimens consisted essentially of bloody inflammatory exudate. In the follow-ups, inflammatory exudate was obtained sooner, indicating that the protective mucosal barrier had been impaired by repeated stimulation.

Influence of Repeated Eugenol Stimulation on the Gastric Mucosa. B. P. SONNENBLICK, H. A. SOBER, AND F. HOLLANDER. *Federation Proc.* 6:292, March, 1947.

Repeated stimulation of Heidenhain pouches with eugenol emulsion was performed on 5 dogs; similar but shorter "follow-up" studies were done after 36 hours and 3-5 months. Smears of each specimen were stained metachromatically with toluidine blue. Only columnar cells were observed in smears of the earliest samples; thereafter, these diminish paralleling a decrease of mucin-like substances. Mucous neck chief cells and leucocytes appear in later specimens. A few parietal cells are observed in most samples. Blood, usually hemolyzed, increases with repeated irritation. The later specimens consist of bloody inflammatory exudate predominantly, with few cells and little mucin. The "follow-ups" indicate that the mucosa does not completely recover its original state, even after 3 months.

Treatment of Early Syphilis by the Twenty-six Week Mapharsen-Bismuth Schedule. T. H. STERNBERG AND W. LEIFER. *Am. J. Syph., Gonor. & Ven. Dis.*, 31:124, March, 1947.

Analysis was made of the records of 3,000 soldiers treated for early syphilis with 40 mapharsen and 16 bismuth subsalicylate injections in 26 to 38 weeks. About 87 per cent of patients were observed for nine months from inception of treatment, and about 72 per cent for 12 to 36 months. The observed failure rate was 1.75 per cent in 1,296 seronegative primary cases; 5.52 per cent in 1,131 seropositive primary cases; and 10.66 per cent in 411 secondary cases. There was 0.64 per cent of abnormal spinal fluids among 2,824 examined after treatment, and there were three cases of symptomatic neurosyphilis. The failure rate in Negro patients was 5.3 per cent, and in white patients 3.7 per cent. It was estimated that approximately 1 in 33,000 patients died as a direct consequence of treatment.

Myelosclerosis with Leukoerythroblastic Anemia. M. L. SUSSMAN. *Am. J. Roentgenol.*, 57: 313, March, 1947.

Nine cases are reported and illustrated in which myelosclerosis was demonstrated roentgenologically in instances of leukoerythroblastic anemia. Differentiation from other conditions associated with myelosclerosis is not difficult when full clinical data are available. Although the disease may be chronic, there is usually progression into frank leukemia as seen at postmortem examination.

Injectional Treatment of Internal Hemorrhoids. R. TURELL. *Am. J. M. Sc.*, 213: 350, March 1947.

The author shows that injectional therapy is effective in a large percentage of patients suffering from small to medium-sized internal hemorrhoids which may or may not be associated with spontaneously reducible prolapse. This is an economical office procedure which is neither simple nor without danger. The therapeutic success (cessation of bleeding and correction of associated prolapse) depends to a great extent on the patient's cooperation. As a result of this study operation is not applied to the treatment of small or medium-sized internal hemorrhoids, but is reserved for the treatment of large internal, for interno-external (mixed) hemorrhoids, and for hemorrhoids that are associated with or complicated by anorectal lesions that require surgical excision.

Buphthalmis in a Six Month Premature Infant. D. WEXLER AND A. L. KORNZWEIG. *Arch. Ophth.*, 37: 318, March, 1947.

This case, in a 6 months premature infant, affords an opportunity to study congenital glaucoma in microscopic section at an earlier stage than has been hitherto possible. Two hours after delivery, the left eye was found to be stony hard. Compared with the eye of a normal 6 months fetus, the glaucomatous eye was considerably enlarged in all its diameters. The iris was in intimate contact with the cornea in its entire extent, separated from Descemet's by a distinct bluish-staining membrane, which could be traced from the pupillary edge to the iris root. A definite trabeculated structure in the position corresponding to the angle was lacking. No evidences of inflammation were seen and it is not likely that inflammation was an influence in the non-development of the trabeculated structure in the angle.

Vitamin Problems in Oral Pathology. D. ADLERSBERG. *New York State Dent. J.*, 13: 181, April, 1947.

Some observations in nutrition have been misinterpreted by confusing the effect of vitamins with that of trace elements. Remarkable changes, e.g. prevention or promotion of growth, can be effected by withdrawing or adding minute amounts of iron, manganese, mercury, boron, copper, zinc, etc. In the eastern part of the country, we rarely encounter fully developed primary nutritional deficiencies like beri-beri, pellagra and scurvy. We are mostly concerned with secondary or conditional deficiencies in association with other diseases. The secondary deficiencies may be caused by malabsorption or poor utilization of all essential nutrients, proteins, carbohydrates, fats, vitamins, and minerals, e.g., by gastrointestinal disorders, after operations, especially resections of the gastrointestinal tract, after severe febrile disease, excessive use of cathartics, etc. As a rule, our patients present only mild forms of nutritional deficiency (subclinical or subcritical form). The oral structures are visible indicators of the nutritional status of the individual. Careful examination of these structures is essential for diagnosis and therapy of nutritional deficiencies.

Nontumid Ileocolic Intussusception in an Adult. Report of a Case with Cecal Ulcer. L. BLUM. *Surg. Clin. North America*, New York No., p. 355, April, 1947.

Intussusception in the adult is invariably associated with the presence of a tumor. This is a report of a case in which there was no evident exciting anatomic factor. The etiology is discussed in terms of the more popular theories and a suggestion is made that a sympathetic

dyskinesia might serve as the mechanism for the origin of this condition in the absence of a tumor. The clinical and roentgen data in diagnosis are revealed.

Peptic Ulcer as a Psychosomatic Disease. B. B. CROHN. Surg. Clin. North America, 27: 309, April, 1947.

More and more today the concept of peptic ulcer as a disease associated with psychosomatic disturbances is gaining ground. The hypothalamus controls gastric motility and gastric secretion. Experimental work has proven that. Clinically one cannot prove that ulcers originate *de novo*, but in the clinical practice there are so many examples of recurrence of ulcer initiated by anxiety, that the relationship is convincing. Ulcer pains recur, hemorrhages are induced by emotional strain, by psychic emotion, and by continued mental perturbation. Striking examples of this relationship are quoted.

Spontaneous Rupture of the Common Bile Duct Following Choledocholithotomy. D. A. DREILING. Surg. Clin. North America, New York No., p. 381, April, 1947.

A case of spontaneous post choledocholithotomy choledochal rupture is presented. The literature, etiology, and prevention of this surgical complication are discussed. Mechanical and functional obstruction are stressed as the causative factors. Increased intra-choledochal tension due to calculus obstruction and the effects of pancreatic reflux were considered the etiological factors in the case presented. There was also some suggestion that spasm of the sphincter mechanism might also have been involved in elevating the intraductal tension sufficiently to produce rupture at the weak point of the biliary tract, i.e., the site of previous surgery. Evidence in the literature is presented which suggests that sphincter spasm may not be merely a contributing mechanism but the sole etiological factor in spontaneous rupture of the common bile duct. The surgeon is cautioned against the use of morphine in the post-operative period following surgery of the biliary tract because of the intense spasm it produces in the sphincter of Oddi.

Compulsory Prepaid Medical Care. E. P. BOAS. J. Pediat., 30: 478, April, 1947.

Good medical care should be universally available, yet it is financially out of reach of many of our citizens. The rapid increase of chronic diseases that has resulted from the ever-growing control of the infectious diseases has brought about a reorientation of public health activities. The only way to control the chronic diseases is through early diagnosis and treatment, i.e. by making medical care readily available to all. Voluntary insurance plans can never meet the needs of the bulk of our population. These can be met only by governmental compulsory prepayment insurance. With such prepayment and with medical service delivered by organized groups of physicians, paid by the insurance fund, medicine would be left free, and good modern medical care would be available to everyone.

Salmonella Typhi Murium Cholangitis Treated with Streptomycin. D. A. DREILING. Surg. Clin. North America, 27: 373, April, 1947.

A case of salmonella typhi cholangitis treated with streptomycin and surgery is presented. The patient had had salmonella gastroenteritis previous to her illness which started with the abrupt onset of chills, fever and obstructive jaundice. The patient was treated at first with cholecystostomy and then choledocholithotomy. Salmonella typhi murium was isolated from the common duct drainage. The infection persisted despite adequate internal and external biliary drainage and despite treatment with sulfonamides and penicillin in adequate dosage. The organism was found to be susceptible to streptomycin over a course of 5 days. Although adequate levels were obtained in the blood, the concentration in the bile was below the susceptibility of the organism. Despite this, the patient went on to a dramatic clinical response even though she did not obtain bacteriological cure. High dosage and prolonged treatment with streptomycin are advised to eradicate biliary infections due to susceptible organisms.

Hemagglutination with Newcastle Disease Virus (NDV). A. L. FLORMAN. Proc. Soc. Exper. Biol. & Med., 64: 458, April, 1947.

Newcastle disease of fowl is an acute infection associated with severe intestinal, respiratory and nervous symptoms. The virus which causes this disease is capable of producing hemagglutination. In a study of the phenomenon of hemagglutination, it was found that the methods which had been developed for influenza viruses were not satisfactory with NDV. Hemagglutination by NDV is markedly affected by temperature. At room temperature the reaction is difficult to read, especially with low dilutions of virus. At 4° C. the reaction is easily read and titration endpoints are readily determined. At 4° C. NDV appears to be adsorbed more completely by and to elute less rapidly from chicken red cells than at room temperature. Details of satisfactory methods for titration of virus and antibodies against it are presented. Both tests are carried out at 4° C.

Operation for the Cure of Incontinence of Urine in the Female. R. T. FRANK. Am. J. Obst. & Gynec., 53: 618, April, 1947.

Incontinence of urine in the female can be cured by a simple technic if all of the available structures are employed in reconstruction. These include the fascia propria of the bladder, the pubo-cervical layers of the endopelvic fascia and the remains of the triangular ligament. The operative technic is described and illustrated by 5 figures. Twenty-three cases are reported, some in detail.

Inhibitory Effect of Dibenamine on Vasoconstrictor Substances. H. HAIMOVICI. Proc. Soc. Exper. Biol. & Med., 64: 486, April, 1947.

The possible clinical usefulness of Dibenamine (N,N dibenzyl-beta-chloroethyl amine hydrochloride) in angiospastic conditions associated with peripheral vascular diseases, causalgic states or hypertension, prompted an investigation of vasomotor responses to this new adrenergic-blocking agent, as expressed in terms of peripheral blood flow. Using the Lacwen-Trendelenburg preparation in frogs as a test object, it appears that Dibenamine is a powerful inhibitor of the vasoconstrictor action of epinephrine. Its adrenolytic action is very potent, for it blocks even large amounts of epinephrine (50-1000 γ). When the action of large amounts of epinephrine is completely inhibited by Dibenamine, both hypertensin (angiotonin) and nicotine still exhibit a marked vasoconstrictor activity. The peripheral locus of action of Dibenamine seems to be at the neuroeffector cells or between the post-ganglionic nerve endings and the latter.

Are Gastric Ulcer and Duodenal Ulcer Different Diseases? F. HOLLANDER. Surg. Clin. North America, 27: 265, April, 1947.

The physiological as well as clinical differences and similarities of gastric and duodenal ulcer are discussed. Clinical considerations include: volume of gastric juice produced, its acid and pepsin concentration, motor disturbances, ulcer size, and pain. Several mechanisms that have been advanced to explain these differences are compared; i.e. a neural (psychosomatic) theory and one based on a duodenal deficiency in enterogastrone. It is concluded that duodenal and gastric ulcer must be considered as the same disease until further and more definitive evidence, clinical and physiological, is found to the contrary.

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*THE EDWARD GAMELIEL JANEWAY LECTURE**
 THE NEWER ANTIBIOTICS: POLYMYXIN, CHLOROMYCETIN, AND
 AUREOMYCIN^{1, 2, 3}

EMANUEL B. SCHOENBACH, M.D.

Associate Professor of Preventive Medicine, Associate Professor of Medicine, Johns Hopkins University School of Medicine; Physician, The Johns Hopkins Hospital

[Baltimore, Md.]

It is indeed an honor and a privilege to have been invited to present the Edward Gameliel Janeway Lecture tonight. Previous speakers, whom I have had the pleasure to hear, have all been distinguished scientists and clinicians. Upon reflection, my trepidation and awe were somewhat allayed, however, when I realized that the topic would encompass a group of antibiotics which have only recently been discovered and, therefore, no erudition on my part was implied.

Dr. Janeway believed that the art of medicine, like civilizations, either advanced or disintegrated. It is a pleasure, therefore, to review the recent investigations which may have contributed to the treatment of some infectious diseases.

The brilliant success which followed the introduction of the sulfonamides, penicillin, and streptomycin, as chemotherapeutic agents for numerous bacterial infections, while gratifying, did not result in complacency, but rather served to stimulate the search for newer antibiotics. Those infections which did not respond to the known therapeutic agents, including a large segment of infectious diseases caused by rickettsiae and viruses, assumed a position of prominence and the problems of toxicity, host-sensitivity and the development of resistance by micro-organisms were intensively investigated.

During the past two years, two new groups of antibiotics have been described. One group derived from filtrates of *B polymyxa* (polymyxin) has been found to

* Presented at the Blumenthal Auditorium, The Mount Sinai Hospital, April 11, 1949.

¹ Polymyxin D and Aureomyein were kindly supplied by the Lederle Laboratories Division American Cyanamid Company; Polymyxin B by the Burroughs Wellecome and Company Inc.; and Chloromycetin by Parke, Davis and Company.

² The original investigations presented were conducted in the Department of Medicine and the Department of Preventive Medicine, The Johns Hopkins University School of Medicine in collaboration with Drs. Morton S. Bryer, Caroline A. Chandler, Eleanor A. Bliss, and Perrin H. Long. The sincere and generous cooperation of the House Staff and Attending Staff of many hospitals, especially the Johns Hopkins Hospital, the Sinai Hospital, and Sydenham Hospital in Baltimore, was a distinct contribution to these studies. The inestimable aid of Mr. C. Earl Ott of the Department of Preventive Medicine, who assisted in the experimental procedures and prepared the illustrations, is gratefully acknowledged.

³ These investigations were supported by grants from the Abbott Laboratories, Lederle Laboratories Division American Cyanamid Company, Parke, Davis and Company, the Upjohn Company and the American Cancer Society.

be highly active upon gram-negative micro-organisms. The other group consists of two chlorinated antibiotics, chloromycetin and aureomycin, which have been found effective in infections caused by gram-positive and gram-negative micro-organisms in addition to those due to rickettsiae and certain viral agents. Our group in the Department of Preventive Medicine has had the good fortune to be associated with the development, and early clinical trial of these antibiotics.

The polymyxin group possesses certain undesirable toxic properties which preclude their general use. Aureomycin and chloromycetin have already been released and are available for therapy.

POLYMYXIN

In May, 1947, Benedict and Langlykke (1) reported that sterile culture filtrates of *Bacillus polymyxa* in dilutions of 1:1000 inhibited the growth of *Brucella bronchiseptica*. Shortly thereafter, Stansly, Shepherd, and White (2) independently described the isolation of an antibiotic substance from *B. polymyxa* which they named "polymyxin". This antibiotic was shown by them to be effective *in vitro* only against gram-negative organisms and to possess a high degree of therapeutic activity against experimental infections. Subsequently, Stansly and Schlosser (3) established the identity of polymyxin as a new antibiotic and developed a method for its bio-assay (4, 5). During the same period, Ainsworth, Brown, and Brownlee (6) described an antibiotic derived from cultures of *Bacillus aerosporus* Greer which was active against gram-negative organisms. They named this antibiotic "aerosporin". It was noted that *Bacillus Aerosporus* Greer was probably the same as *B. polymyxa*.

Some confusion in nomenclature has resulted from the numerous designations given the different preparations obtained from strains of *B. polymyxa*. It has been generally agreed that the antibiotic described by Stansly, et al, would be designated as polymyxin D, while the original aerosporin would be called polymyxin A. Several other antibiotics isolated by the British workers have been designated as Polymyxin B and C (7). A new preparation, polymyxin E, has been prepared but has not been made available for study.

All these polymyxins are basic polypeptides with a molecular weight which varies between 1000 and 1300. They all contain a C-9 fatty acid, L-alpha-gamma-diamino butyric acid and L-threonine. D-serine has only been identified in polymyxin D, L-phenylalanine in polymyxins B and C, while D-leucine is present in polymyxins A, B, and D (7).

The pharmacology of polymyxins A, B and D has been reported (2, 7-15). The *in vitro* activity of polymyxin D, when tested against gram-negative organisms, is presented in a chart in which the results observed with chloromycetin and aureomycin are included. The action of polymyxin B is essentially equivalent. End points in titrations are clear cut without further shift on prolonged incubation. This observation plus studies of growth curves indicate that polymyxin is bactericidal in concentrations above 0.3 micrograms per milliliter when a uniform inoculum of approximately 100,000 *E. coli* organisms is used. The

end point observed, will vary, however, when the size of the inoculum is varied. Polymyxin is most effective in an acid medium. Activity is not markedly impaired in the presence of serum. Attempts to produce resistant strains have been unsuccessful. Most strains of *E. coli*, aerobacter, and Friedländer bacilli are susceptible to 0.3 micrograms of polymyxin per milliliter. *H. influenzae* type B is equally susceptible. *Pseudomonas aeruginosa* requires 2.5 micrograms per milliliter to achieve sterility while strains of proteus and meningococci are resistant *in vitro*. Aqueous emulsions of soy bean lecithin and lipositol interfere with the anti-bacterial action of polymyxin. Gram-positive organisms are completely resistant. In our experience, polymyxin has approximately two to eighty times the activity of streptomycin against susceptible bacteria when tested *in vitro* (9, 13).

TABLE 1
Chemical Composition of Polymyxins A, B, C, and D

COMPOSITION	POLYMYXINS			
	A	B	C	D
D-Leucine	+	+	0	+
L-Phenylalanine	0	+	+	0
D-Serine	0	0	0	+
L-Threonine	+	+	+	+
L- α - γ -Diamino Butyric Acid	+	+	+	+
C ₉ H ₁₅ O ₂ (Fatty Acid)	+	+	+	+

Polymyxin D is moderately toxic for mice. The subcutaneous LD 50 is 250-300 mg/kg, when administered as a single dose. Dogs have tolerated 10 mg/kg administered intramuscularly twice daily for seven days but a single injection of 15 mg/kg given intravenously caused profound symptoms and 25 mg/kg resulted in death. The reactions noted were incontinence, slowing of respiration, paresis, and tremor. Apnea and paralysis preceded death. Intrathecal administration of five or ten milligrams of polymyxin dissolved in a special buffer, pH 7.4, and diluted with spinal fluid caused transient paralysis (10, 14).

Young female rats with normal urine developed cellular casts and albuminuria 24 hrs. after a single subcutaneous injection of 20 mg/kg of various types of polymyxin. The specific gravity of the urine was markedly reduced. The albuminuria and casts appeared to diminish even though polymyxin administration was continued. Simultaneous administration of dl-methionine, 50 mg/kg parenterally, and 1.0% of the diet orally, did not prevent the urinary changes. No decrease in body weight or in the hemoglobin content of the blood was observed (14).

Microscopic examination of the kidneys of mice, dogs, and rats receiving polymyxin revealed damage to the tubular epithelium. When massive doses of 250 to 300 mg/kg were injected, marked necrosis of tubular epithelium and tubular casts were observed.

Following a single intramuscular dose of 5 and 10 mg/kg of polymyxin, serum levels of 2.5 and 5.0 micrograms per milliliter were observed in dogs. These levels were well maintained and three and one-half hours after the injection, levels of 1.25 to 2.5 micrograms were still present. When the drug was injected twice daily for seven days, the serum levels attained were considerably increased and were maintained for approximately five hours following the last injection. Levels were still detectable 23 hours later. Despite the high levels attained

TABLE 2
Assay for Polymyxin D in Body Fluids in Dogs

ROUTE OF ADMINISTRATION	DOSAGE SCHEDULE	SPECIMEN EXAMINED	INTERVAL POST LAST INJECTION	LEVEL OF "POLYMYXIN" GAMMA/CC
Intramuscular	5 mg/kg single dose	Serum	90 Minutes	2.5
			150 Minutes	2.5
			210 Minutes	2.5
	10 mg/kg single dose	Serum	90 Minutes	5.0
			150 Minutes	2.5
			210 Minutes	1.25
	5 mg/kg B.I.D. for 7 days	Serum	15 Minutes	10.0
			30 Minutes	20.0
			60 Minutes	20.0
			180 Minutes	10.0
			5 Hours	2.5
			23 Hours	0.0
	10 mg/kg B.I.D. for 7 days	Serum	15 Minutes	20.0
			30 Minutes	20.0
			60 Minutes	20.0
			180 Minutes	20.0
			5 Hours	2.5
			23 Hours	0.125
	5 mg/kg B.I.D. for 5 injections	Serum	65 Minutes	2.5
		Sp. Fl.	65 Minutes	0.0

both by intramuscular and intravenous routes of administration, no polymyxin was detected in the spinal fluid. When the polymyxin was administered intraspinally in doses of 1, 5, and 10 milligrams, levels of 10 to 500 micrograms per milliliter were obtained. Detectable blood levels followed intrathecal administration (14).

The therapeutic effectiveness of polymyxin was assayed in mice experimentally infected with *K. pneumoniae* type A and *H. influenzae* type B. When 1000 lethal doses were administered intraperitoneally, blood cultures were positive in all animals 24 hrs. post infection and the animals all died within 18 hrs. 50 milligrams of polymyxin D per kilogram of body weight injected subcutaneously protected the mice, and blood cultures were sterile at 4 and 18 hrs. One milli-

gram per kilogram injected subcutaneously protected the majority of the mice and the protection demonstrated was equal to that noted with 5 to 10 mg/kg of streptomycin similarly administered. When treatment post infection was delayed, larger doses of polymyxin were found necessary to permit survival. The discrepancy between polymyxin and streptomycin became even more apparent. Fifty milligrams per kilogram of polymyxin administered five hours post intraperitoneal infection with 10,000 lethal doses of *K. pneumoniae* type A was required to achieve the protection observed when 1.0 mg/kg was injected immediately after infection. No survivors were observed when streptomycin was similarly employed 5 hrs. post infection. No protection of mice infected

TABLE 3
Assay for Polymyxin D in Body Fluids in Dogs

ROUTE OF ADMINISTRATION	DOSAGE SCHEDULE	SPECIMEN EXAMINED	INTERVAL POST LAST INJECTION	LEVEL OF "POLYMYXIN" GAMMA/CC.
Intravenous	Continuous drip 0.25 mg/kilo per minute	Serum	150 Minutes	320.0
		Sp. Fl.	150 Minutes	0.0
Intrathecal	1 mg. L ₄ -L ₅	Sp. Fl.	45 Minutes	10.0
			225 Minutes	0.3
	5 mg. cisternal	Serum	25 Minutes	1.25
			200 Minutes	0.625
		Sp. Fl.	15 Minutes	500.0
			295 Minutes	20.0
	10 mg. cisternal	Serum	20 Minutes	0.0
			125 Minutes	0.625
		Sp. Fl.	15 Minutes	320.0
			120 Minutes	80.0

with gram-positive organisms (*Strep. hemolyticus* Beta C-203, or *D. pneumoniae* type I) was observed when the mice were treated immediately after infection with even 100 mg/kg of polymyxin. 50 mg/kg of polymyxin daily for 6 days had no effect on the development or growth of Sarcoma 180 in mice (16).

The unique antibacterial activity of polymyxin and the protection of experimentally infected animals with doses far less than those at which toxic manifestations were noted, were deemed sufficient evidence for careful circum-spect clinical trial. It was hoped that data might be assembled which would indicate the potentialities of polymyxin and thus stimulate adequate production and purification. A small series of patients was treated. The varied types of infection and the great difference in age of these patients render any generalization or statistical analysis untenable. The gram-negative infections differ markedly from most gram-positive infections in that complications, such as an underlying dermatitis, neoplasm, burn, etc., which aid in initiating or maintaining the infections, may be present. Thus the clinical course of the untreated patient

is difficult to predict and that of the treated patient to evaluate. Resort to bacteriologic procedures coupled with objective clinical observations of each case is necessary.

COMPARISON OF POLYMYXIN & STREPTOMYCIN

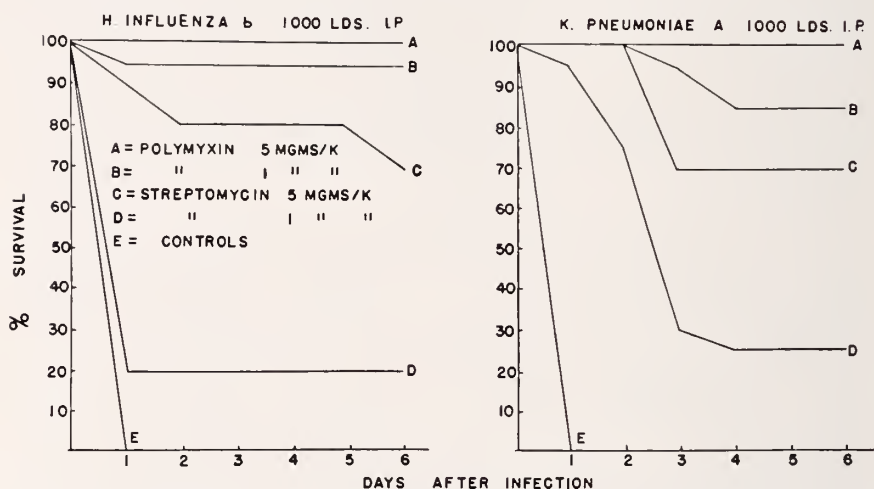


FIG. 1. Protection of mice infected intraperitoneally with 1000 lethal doses of influenzae B and K. pneumoniae A, who were treated soon thereafter with polymyxin D or streptomycin. The superiority of polymyxin is evident.

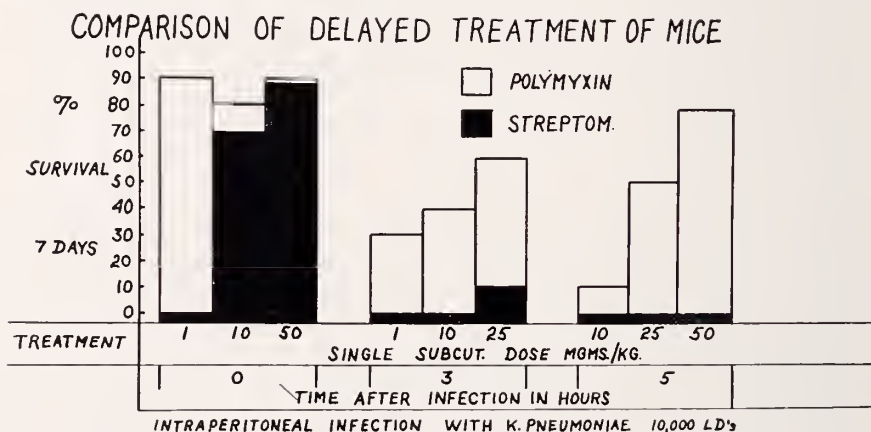


FIG. 2. Comparative protection of mice with polymyxin D and streptomycin when treatment was delayed for three and five hours after injection.

The dosage schedule of polymyxin employed in these trials varied from 3.0 to 7.0 mg/kg daily, divided into three to eight doses. The larger amounts of polymyxin were not tolerated for more than a few days and the dose was then reduced to 3-4 mg/kg per day. A concentration of 60 to 120 mg in two milliliters of diluent was well tolerated. Polymyxin D was administered intra-

muscularly in a phosphate buffer pH 7.4 but no buffer was necessary for Polymyxin B. At the higher concentration of drug, some dull drawing pain was experienced at the local site of injection. However, almost all patients preferred this discomfort to two doses of more dilute material. The injections were not discontinued in any patient, either 6 weeks or 62 years of age, because of local intolerance. No intravenous administration was attempted.

Results: Patients were treated with polymyxin for periods up to 20 days. The blood levels attained, when the drug was given every three hours at a dosage level of 3mg/kg per day, was 0.6 to 1.3 micrograms per milliliter of serum, 12 hrs. after therapy was instituted. On continued treatment, these levels rose to 2.5 to 5.0 micrograms per milliliter on the 5th to 10th day. When 7.0 mg/kg

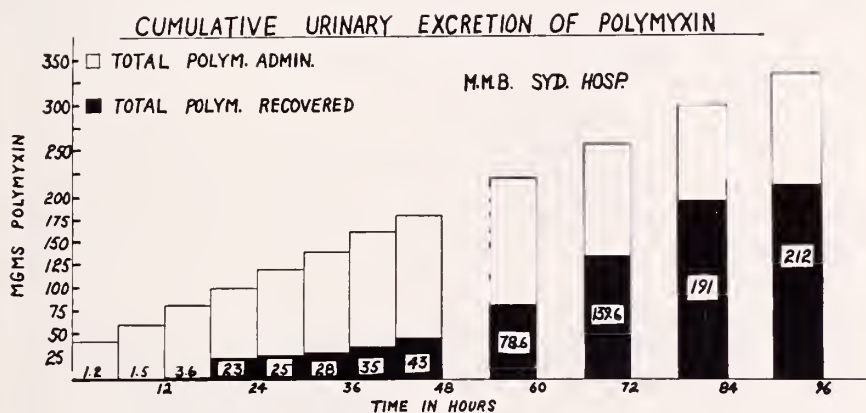


FIG. 3. Cumulative urinary excretion of polymyxin D with constant intramuscular administration.

per day were given in divided doses, levels were higher and the variation between pre- and post-injection specimens was greater. Serum levels of 5.0 to 10.0 micrograms per milliliter were observed which rose to 20 or more micrograms one hour after an injection of 2.0 mg/kg. Because of difficulties in the biologic titration, these levels are only presented as approximate indications and are not strictly quantitative.

No polymyxin was detected in the cerebro-spinal fluid after intra-muscular administration, even in the presence of a purulent meningitis. Intrathecal administration through the 4th lumbar interspace of 2.0 mgs., resulted in a concentration of 5.0 micrograms per milliliter 12 hrs. later in fluid obtained by cisternal puncture.

When daily amounts of 4-7 mg/kg of polymyxin was administered intramuscularly, a lag in urinary excretion for approximately twelve hours was observed. Drug then appeared in the urine in increasing amounts, so that by 72-96 hrs. approximately 60 per cent of the administered drug had been excreted. The outstanding complication noted with polymyxin D was renal damage. Albuminuria, casts, and large epithelial cells appeared on the third to fourth day of therapy. This has been noted in the majority of the treated patients. The

albuminuria was heralded by a change in pH of the urine from acid to alkaline reaction. The specific gravity of the urine approached 1.010 and loss of concentrating ability was evident. Four patients developed azotemia and, in one of these patients, a marked diminution in urinary volume was observed. This low incidence, among gravely ill patients who often showed evidence of renal impairment before polymyxin therapy was instituted, encouraged us to hope that further purification might eliminate this toxic manifestation. Further studies with more highly purified and different preparations have been fruitless to date. Polymyxin B has been observed to cause fever and somnolence in addition to the renal toxicity.

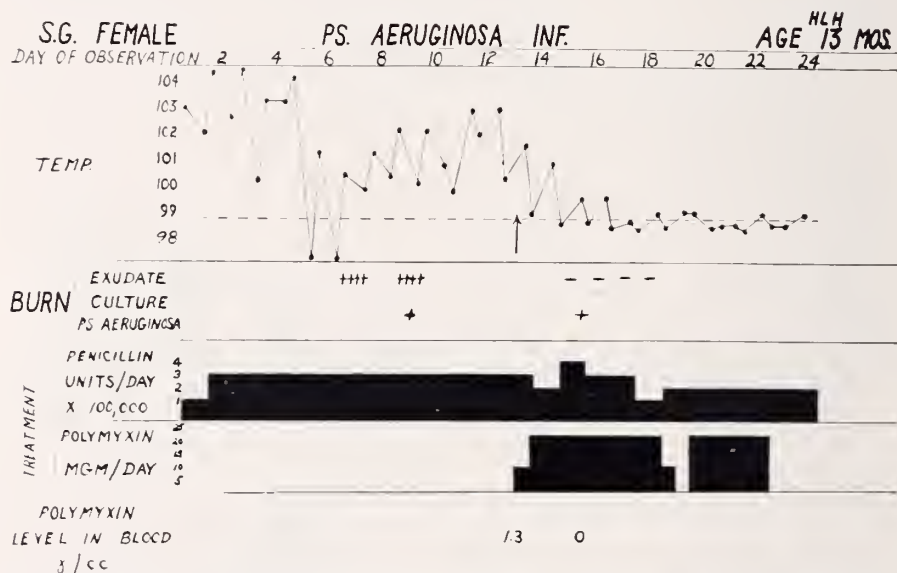


FIG. 4. *Pseudomonas aeruginosa* infection of a severe third degree burn involving twenty-five per cent of the body area and second degree burns of the face, buttocks, thighs, calves, and elbows. The child was gravely ill with temperature of 104°F. and convulsions. Infection cleared rapidly and successful skin grafting was performed six days after polymyxin treatment was begun.

Several patients, desperately ill with *Pseudomonas aeruginosa* (*B. pyocyaneus*) infections have shown a prompt response to therapy with polymyxin after streptomycin, penicillin, and sulfonamides had been ineffectual. Three cases of pseudomonas meningitis have been cured. This response has not been uniform, however. One case of meningitis and a severe urinary tract infection in an infant with multiple congenital abnormalities showed no improvement. Despite its toxicity, treatment with polymyxin would appear to be warranted for this type of septicemia. When used topically as a 0.1 per cent solution, polymyxins B and D appeared to exert a favorable effect on the local infection.

Three cases of aerobacter aerogenes bacteremia were treated with polymyxin. Blood cultures became sterile in two patients within twenty-four hours after onset of therapy and the patients became afebrile. The third patient, an acute

endocarditis treated for only 60 hours, showed a marked reduction in fever and the number of colonies isolated from her blood almost disappeared. She died in

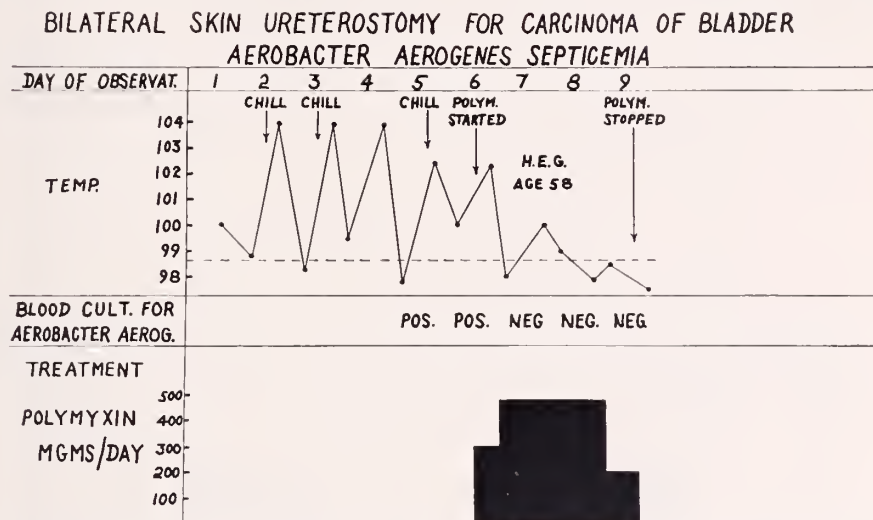


FIG. 5. Prompt response of an *A. aerogenes* septicemia secondary to a urinary tract infection and treated with polymyxin D. The patient was a 58 year old man with a bilateral skin ureterostomy performed for carcinoma of the bladder.

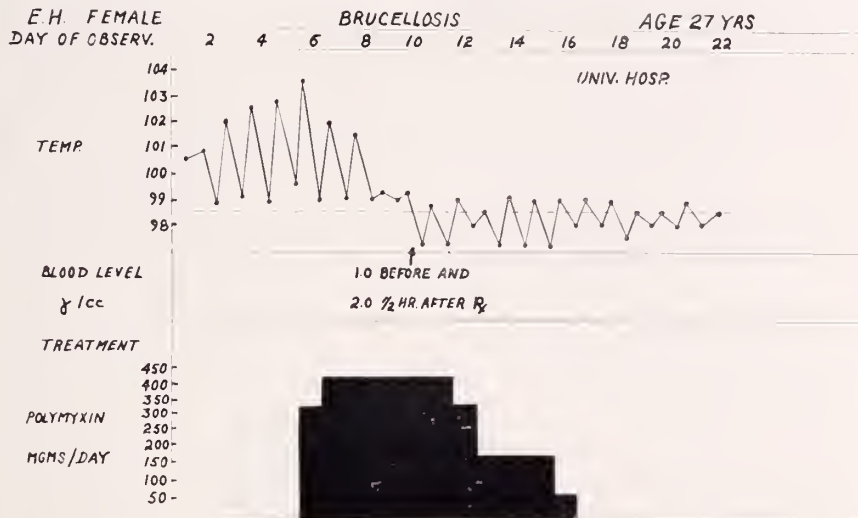


FIG. 6. Response of a 27 year old female patient with acute brucellosis following treatment with polymyxin D. Patient remained asymptomatic.

congestive heart failure too soon after institution of therapy for proper evaluation. One case of peritonitis secondary to a perforated appendix became afebrile within three days and convalescence was uneventful.

Three cases of acute brucella infection were treated with polymyxin for a period of 10 days. These patients experienced rapid relief of symptoms and became

afebrile within 3 to 4 days. One patient relapsed one month later and was then treated with aureomycin. Sulfadiazine plus streptomycin had been completely

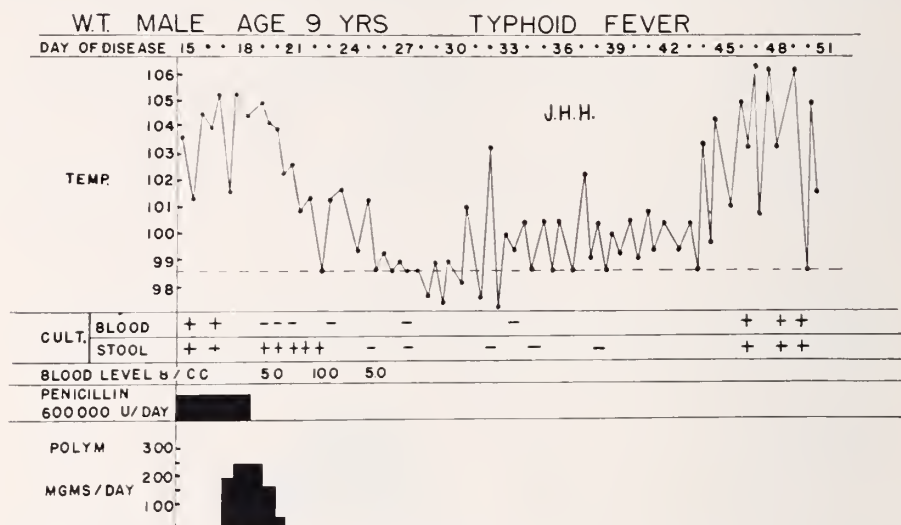


FIG. 7

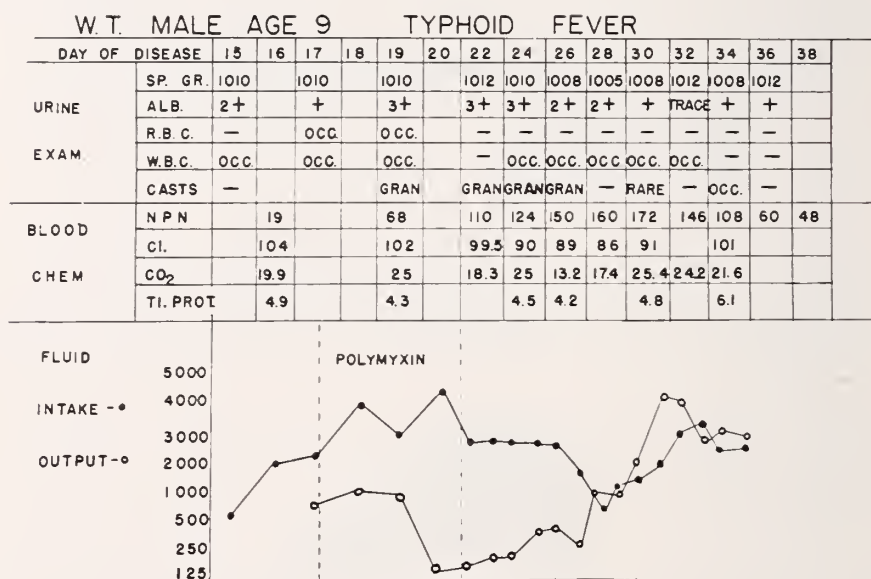


FIG. 8

FIGS. 7 and 8. Illustrates the course of typhoid fever in a nine year old boy treated with polymyxin D who developed marked oliguria and azotemia while receiving polymyxin from the seventeenth to the twenty-first day of disease. Renal damage, present before therapy, was markedly aggravated. Child eventually recovered completely.

ineffective in this patient and blood cultures had remained positive until polymyxin was administered. A fourth patient with chronic brucellosis did not experience any real improvement with polymyxin.

Three cases of typhoid fever and a persistent biliary carrier were treated with polymyxin. One patient was in extremis when treatment was begun and he died 48 hrs. later, in the fourth week of his illness, without evident benefit from therapy. Another patient developed a severe oliguria and treatment had to be

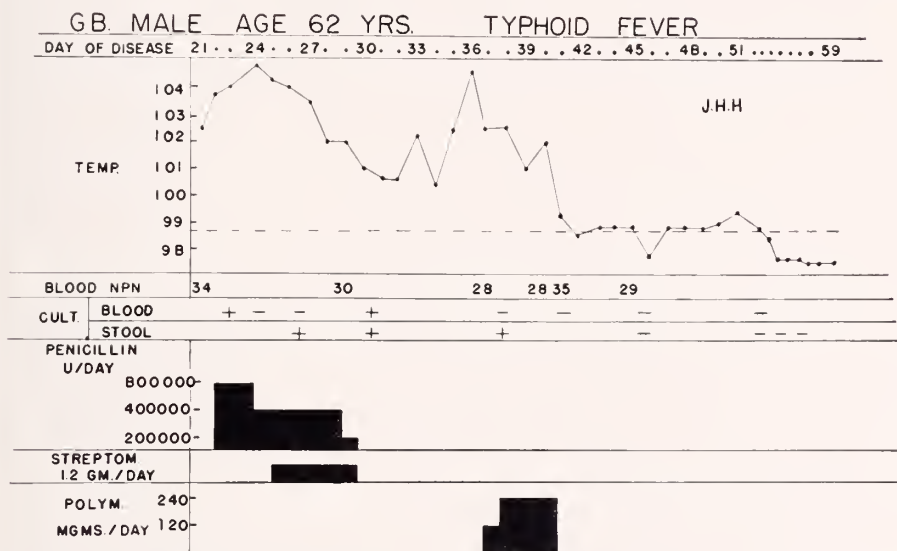


FIG. 9. A 62 year old male with pneumonia, phlebitis, benign prostatic obstruction, and typhoid fever treated with polymyxin D. Recovery was uneventful.

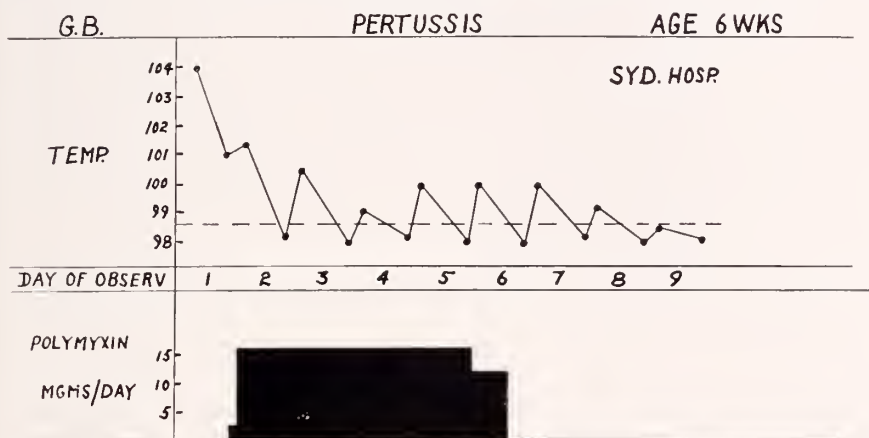


FIG. 10. Six week old infant, whose older brother was under observation with pertussis was treated on the fourth day of his disease with prompt remission of fever and symptoms within thirty-six hours. The infant was considered extremely ill when admitted.

discontinued. He recovered his renal function but suffered a relapse of his disease. The chart of this patient is presented. A 62 yr. old male with right lower lobe pneumonia, phlebitis, and prostatic obstruction was discovered to have typhoid fever. Treatment with polymyxin for five days resulted in rapid clinical recovery and blood and stool cultures became negative. A transient increase in albuminuria unaccompanied by azotemia was noted. One month

later, a suprapubic prostatectomy was performed and the patient experienced an uneventful convalescence. A persistent typhoid carrier with a biliary fistula was treated with polymyxin and the biliary cultures became and remained negative after twenty-four hours.

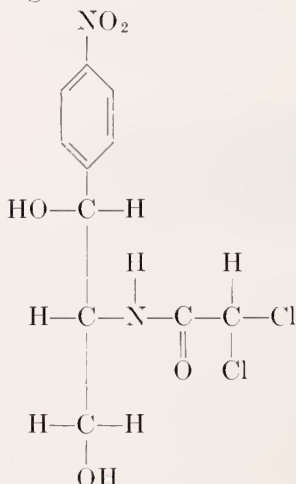
The effect of polymyxin D in pertussis is difficult to evaluate because of the variation in clinical course and bacteriologic findings. Young infants, with known exposure, who were treated early, appeared to benefit from this therapy. Swift has described his preliminary observations with polymyxin A (17). The most critical and extensive study on the treatment of pertussis with polymyxin B has been made by Kaplan, Fischer, and Kohn (18). The toxic reactions encountered far outweighed any distinct amelioration of the disease.

In addition, a number of other gram-negative infections due to *K. pneumoniae*, salmonella, and shigella, have been treated with parenteral or oral polymyxin. The results have not been uniform or dramatic.

Summarizing the status of the polymyxins it may be said that they do possess many advantageous antibacterial properties but the associated toxicity is of such nature that, at present, they cannot be considered as satisfactory chemotherapeutic agents. In patients gravely ill with pseudomonas infections and who have not responded to other therapy, administration of polymyxin may be followed by dramatic improvement.

CHLOROMYCETIN

Chloromycetin was first isolated by Burkholder (19) in 1947 from a strain of streptomyces. Another strain of streptomyces isolated at the University of Illinois has been found to produce an identical antibiotic (24, 25). The chemical name proposed by investigators at the Parke, Davis Co. for this antibiotic is Chloramphenicol (21-23). The strains of streptomyces have been designated streptomyces venezuela N. sp. (26). Subsequent study and purification have established its constitution as a chlorinated aromatic nitrogen-containing compound (20-23). It has been synthesized and the structural formula is: Chloromycetin (Chloramphenicol; d-(-)-threo-1-paranitrophenyl-2-dichloroacetamido-1,3 propanediol). Molecular weight 322.



Chloromycetin is a neutral crystalline substance relatively insoluble in water but soluble in propylene glycol, ethyl alcohol, acetone and other organic solvents. It is stable in solution over a pH range of 2-9.

Pharmacology. The parenteral toxicity of chloromycetin has been difficult to assess as the drug was dissolved in propylene glycol or ethanol solutions. The acute intravenous LD 50 for mice has been found at 245 to 300 mg/kg of body weight. Large doses, up to 1000 mg/kg in acacia suspension, administered orally to mice as a single dose and repeated ingestion of 1290 mg/kg per day were tolerated except for weight loss, for two weeks. Daily subcutaneous injections of 400 mg/kg in 20 per cent propylene glycol produced ataxia, weight loss, and death in a few days. Divided subcutaneous doses of 200 mg/kg per day were well tolerated for 11 days. Local ulceration and necrosis were evident at the injection sites. Dogs tolerated intramuscular injection of 70 to 80 mg/kg daily of chloromycetin suspended in peanut oil or propylene glycol for 24 days. They developed an anemia, however (27).

In vitro, chloromycetin exerts a bacteriostatic and, at higher concentration, a bactericidal action on many species of gram-positive and gram-negative organisms. Its activity against the gram-positive species is of a much lower order of magnitude when compared to that of penicillin. Our *in vitro* studies indicate that the minimal inhibitory concentration for the gram-positive cocci tested was 2.5 to 10.0 micrograms per milliliter. Gram-negative organisms of the coli-aerogenes and Friedländer groups were inhibited by 1.25 to 10.0 micrograms per milliliter. Pseudomonas strains were not inhibited by 100 micrograms per milliliter while various strains of proteus bacilli varied in their sensitivity from 3 to 25 micrograms per milliliter (16). The tubercle bacillus (27, 36) was relatively resistant, and fungi and protozoan parasites tested were completely resistant to the action of chloromycetin (27).

Mice were treated with chloromycetin administered subcutaneously after intraperitoneal infection with Strep. hemolyticus Beta, pneumococcus type I and K. pneumoniae type A. Fifty mg/kg of chloromycetin afforded little or no protection against the gram-positive coccid infections in which aureomycin and penicillin were effective in relatively low dosages. The results attained with K. pneumoniae type A were of the same order as those observed with aureomycin but were inferior to those obtained with polymyxin and streptomycin (16). Embryonated hens' eggs and mice inoculated with psittacosis or lymphogranuloma virus or the various types of rickettsiae were protected. Other experimental viral infections such as influenza A, St. Louis encephalitis, rabies, and Newcastle virus were essentially unaffected (27-29).

Chloromycetin was well tolerated when administered orally to normal human adults for periods up to 10 days. Following ingestion of an initial dose of 1.0 gram, and 0.2 grams every four hours, peak serum levels of 5.0 to 10.0 micrograms were detected within two hours. Urinary concentrations of 200.0 micrograms per milliliter were noted at the same time. These levels rapidly disappeared, either through clearance or destruction, so that no blood levels were detected after 6 to 8 hours. (30). In patients ill with typhoid fever and treated with an initial dose of 50 mg/kg of body weight, followed by 0.25 grams every two hours, serum

levels of 40 to 80 micrograms per milliliter were detected during the first twenty-four hours. These levels fell in the ensuing three day period to approximately 20 micrograms per milliliter. Other than occasional nausea and vomiting, no evidence of toxicity has been observed with oral administration (31).

Results: Scrub typhus (32), epidemic typhus (33, 34), and Rocky Mountain Spotted Fever (Eastern type) (35) have been treated with chloromycetin and excellent results have been reported. Twenty-five patients suffering from scrub typhus were treated on the third to eleventh day of illness. They became afebrile in an average period of 31 hrs. and no complications or deaths were observed. Fifteen cases of Rocky Mountain Spotted Fever became afebrile in approximately 2.2 days and no mortality or untoward complications occurred. The results in the treatment of epidemic typhus in Mexico and Bolivia were equally dramatic (33, 34).

Woodward⁴, et al., (30), have reported the beneficial effect of chloromycetin in 10 patients ill with typhoid fever. Blood cultures became sterile in all patients and stool cultures were negative for *E. typhosa* in most cases after treatment was begun. Two patients relapsed with bacteremia after afebrile periods of 10 to 16 days but were cured promptly with a second course of chloromycetin. Serious complications, intestinal perforation and massive hemorrhage, were observed in two cases on the second and fourth afebrile day but no deaths occurred. We have treated three severely ill patients on the 4th and 9th and 17th day of their illness. All three cases showed marked clinical improvement and became afebrile within 96, 48 and 26 hrs. respectively. Blood cultures, positive before treatment in the three patients, became sterile, and no relapse or recurrence of *E. typhosa* in the blood has been observed. The general impression at this time, from the data available, is that chloromycetin is an effective therapeutic agent for the treatment of typhoid fever, although the organism may not be eradicated from the biliary tract or stool. One patient who became asymptomatic and afebrile three days after chloromycetin therapy was begun and in whom treatment was continued for several weeks, experienced a relapse of his disease two weeks after his discharge from the hospital. This relapse was associated with fever, a rash, and positive blood cultures for *E. typhosa*. Administration of chloromycetin was again followed by a prompt remission of symptoms and fever within forty-eight hours. This therapy was continued for two weeks despite the patient's asymptomatic state. Biliary and stool cultures remained positive while under this treatment. The patient experienced an acute cholecystitis and perforation of the gall bladder twelve days after the second discharge from the hospital. Convalescence was uneventful after operation and *E. typhosa* was cultured from the bile and biliary calculi obtained at this time. The relapse rate following chloromycetin therapy of typhoid fever would appear to be similar to that observed in previous years before the advent of this antibiotic.

Urinary tract infections with *pseudomonas aeruginosa* (*B. pyocyaneus*) which

⁴ Dr. T. E. Woodward in a personal communication has treated 21 cases of typhoid fever with similar encouraging response. He has also treated 9 cases of acute brucellosis with chloromycetin with prompt remission of signs and symptoms.

had been resistant to streptomycin, sulfadiazine, and penicillin appeared to respond promptly to chloromycetin therapy. The four patients became afebrile but, in two, pseudomonas was recovered from the urine specimens following treatment. The patients remained asymptomatic. This is of interest as *in vitro* determinations with chloromycetin have demonstrated little or no activity against this species of micro-organisms including the strains obtained from the patients (16).

The usual schedule of oral chloromycetin therapy employed is an initial dose of 50 to 60 mg/kg which may be divided into one to three parts and administered at hourly intervals. Subsequent doses of 5 to 20 mg/kg every four hours may then be employed. The duration of therapy will vary with the specific disease. In the rickettsial diseases, no relapse has been noted when drug administration

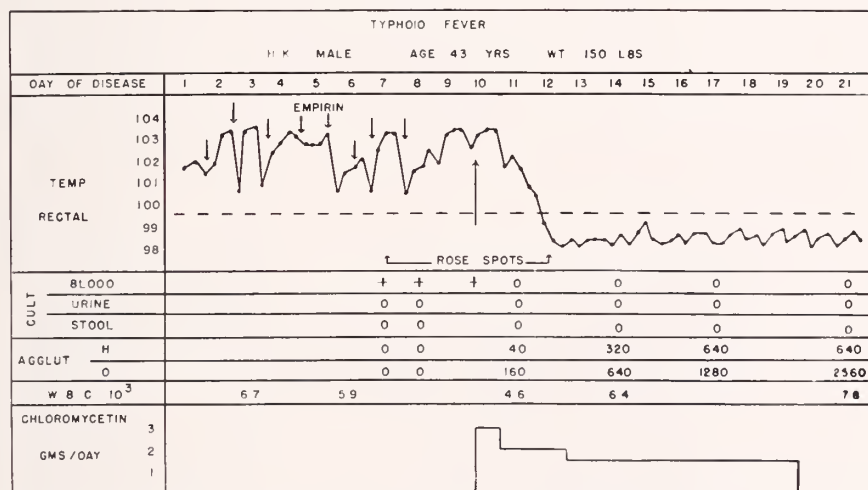


FIG. 11. 43 year old male treated on the tenth day of typhoid fever with chloromycetin. Patient became afebrile in 48 hours and convalescence was uneventful.

is halted after the patient has remained afebrile for 24 hrs. In typhoid fever, a minimal period of 10 to 14 days is advisable. No untoward reactions attributable to chloromycetin have been observed, except for occasional nausea and vomiting. The insolubility of chloromycetin precludes parenteral therapy. Propylene glycol suspensions are not recommended. The drug may be suspended in acacia or syrup and administered by gavage to patients who cannot swallow the capsules.

AUREOMYCIN

Aureomycin is an antibiotic derived from cultures of *Streptomyces aureofaciens* n. sp. first described by Duggar in 1948 (37). The therapeutic potentialities of aureomycin were recognized by Dr. Y SubbaRow at the Lederle Laboratories Division of the American Cyanamid Company who instigated the initial development and experimental investigations. His faith in the antibiotic

persisted despite the early difficulties encountered in the evaluation of aureomycin in the laboratory, and clinical trial, which was attended with such success, was due in large measure to his vision and efforts.

The antibiotic has been crystallized and is a weakly basic organic compound which contains both nitrogen and non-ionic chlorine. A minimal molecular weight of 508 has been determined for this antibiotic. It is unstable in alkaline solution in which loss of antibacterial activity, as well as changes in the ultra-violet absorption spectrum, occur (38).

TABLE 4

Comparison of Chloromycetin, Aureomycin and Penicillin G Activity in vitro against Gram-Positive Cocci

The end points were determined after incubation for 18 to 24 hours

ORGANISM	GRAM POSITIVE COCCI—MINIMAL INHIBITORY CONCENTRATION			
	Chloro	Aureo	Peni.-G	
	<i>Gamma/cc</i>	<i>Gamma/cc</i>	<i>Gamma/cc</i>	
Streptococci				
Beta Group A C203	5	.312	.008	
B 090	5	1.25	.016	
B 19	5	.625	.035	
C K61	5	.625	.016	
D Zymog	10	1.25	2.5	
D 22A	10	.625	2.5	
F For	2.5	.625	.05	
F H59	5	1.25	.016	
Alpha Faecalis				
Bla	10	1.25	2.5	
Tar	10	1.25	2.5	
West	10	1.25	2.5	
Viridans				
Dop	5	.625	.625	
Keel	10	.625	2.5	
Pneumococcus I	SVI	.312	.016	
Staphylococci				
Aureus				
Zeut	5	.625	.062	
Zorn	5	.625	.062	
Gelb	5	.625	.062	
Gibb	10	.625	.012	
Albus	Heatly	5	.625	.012

Pharmacology: *In vitro*, aureomycin possesses marked bacteriostatic and, in higher concentrations, bactericidal properties. The determination of the minimal inhibitory concentrations has been difficult because of the instability of aureomycin in the media at incubator temperature (39-45). When an 18 to 24 hour period of incubation is employed, marked loss of activity occurs and the results obtained represent an integral of the activity present during that period. The growth of gram-positive organisms is inhibited by concentrations of 0.3 to 1.25 micrograms per milliliter. It is considerably less active than penicillin and 4 to 16 times more active than chloromycetin under the conditions

of this test with streptococci, pneumococci, and staphylococci. The Group D streptococci (fecalis) is an exception as aureomycin is more active than penicillin (40). Certain of the gram-negative bacilli (*E. coli*, *A. aerogenes*, *K. pneumoniae*, *H. influenza* type B, and *E. typhosa*) are inhibited by 1.25 to 5 micrograms per milliliter. *Pseudomonas aeruginosa* and most strains of proteus are resistant to 50 to 100 micrograms per milliliter (40)(44). With the exception of the gram-positive cocci and proteus bacilli, the activity *in vitro* of aureomycin and chloromycetin are comparable. Both antibiotics are markedly inferior to polymyxin D with respect to the gram-negative bacilli (16). Eleven recently isolated strains of brucella (abortus and suis types) were sensitive to 0.25 to 0.5 micro-

TABLE 5

Comparison of Chloromycetin, Aureomycin and Polymyxin D Activity in vitro against Selected Gram-Negative Bacilli

The end points were determined after incubation for 18 to 24 hours

ORGANISM	GRAM NEGATIVE BACILLI—MINIMAL INHIBITORY CONCENTRATION		
	Chloro	Aureo	Poly-D
	<i>Gamma/cc</i>	<i>Gamma/cc</i>	<i>Gamma/cc</i>
<i>E. Coli</i> No. 4	5	5	.165
<i>E. Coli</i> No. 9	10	5	.156
<i>E. Communi</i> No. 14	5	5	.625
<i>Citrobacter</i> No. 6	5	5	.625
<i>Aerobacter</i> No. 10	5	5	1.25
<i>Aerobacter</i> No. 12	5	2.5	1.25
<i>Friedlander</i> A	1.25	1.25	.312
<i>Friedlander</i> B	5	5	.625
<i>Pyocyaneus</i> Her	>100	100	1.25
<i>Pyocyaneus</i> Cal	100	100	2.5
<i>Pyocyaneus</i> No. 16	>100	100	.625
<i>Pyocyaneus</i> But	100	100	2.5
<i>Proteus</i> No. 11	<3.1	.625	>100
<i>Proteus</i> No. 17	12.5	50	>100
<i>Proteus</i> No. 18	25	100	>100
<i>Proteus</i> Herr	12.5	100	

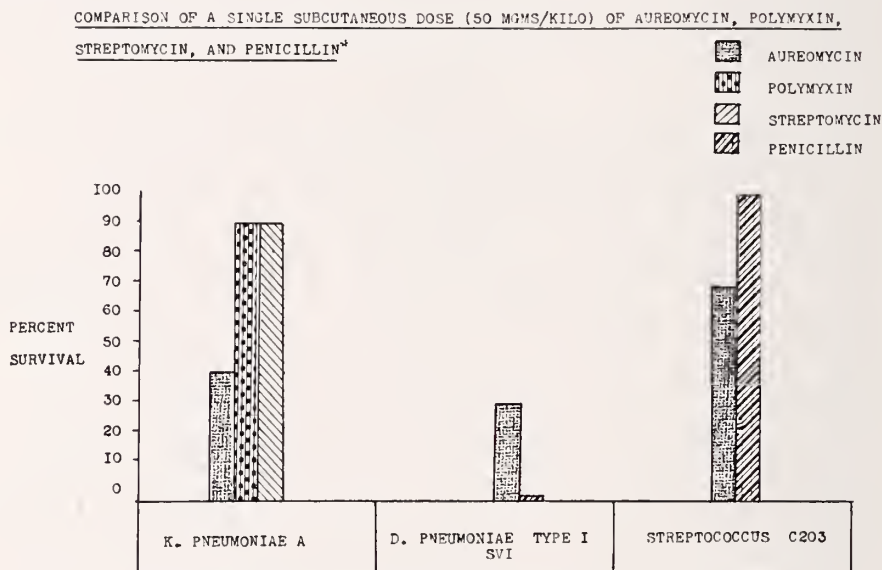
grams per milliliter of aureomycin after 72 hrs. of incubation. After seven days of incubation, the growth of 10 strains of brucella was completely inhibited by 2.0 to 4.0 micrograms per milliliter of medium (46, 53). Resistance to aureomycin does not occur readily.

The acute subcutaneous LD 50 of aureomycin for mice was between 3000 to 4000 mg/kg (46). When the drug was dissolved in a special buffered diluent containing L-leucine and sodium hydroxide, the intravenous LD 50 for mice was approximately 150 mg/kg (16). Orally, mice tolerated 1500 mg/kg and rats 3000 mg/kg administered as a single dose (48).

Repeated daily subcutaneous and intramuscular injections for 8 to 9 days of 40 to 50 mg/kg were well tolerated by rats and dogs except for evidence of local

irritation and mild anorexia and weight loss. No urinary, hematological, or other pathological abnormalities were detected (47).

Aureomycin protected against intraperitoneal infections with virulent strains of gram-positive and gram-negative micro-organisms (47, 49). A single subcutaneous injection of aureomycin was superior to an equal amount of penicillin G in affording protection to mice infected with *D. pneumoniae* type I. When the streptococcus was the infecting organism, the results with both antibiotics were approximately the same. Polymyxin D and streptomycin sulfate



^aALBINO SWISS MICE INFECTED INTRAPERITONEALLY WITH 1000 LD'S OF *K. PNEUMONIAE* A, *PNEUMOCOCCUS* SVI, OR *STREPTOCOCCUS* C203 AND TREATED IMMEDIATELY. SURVIVAL RECORDED FOR 7 DAYS. (10 MICE IN EACH GROUP)

FIG. 12. Comparative protection of mice infected with *K. pneumoniae* A., *D. pneumoniae* type I, and *Streptococcus hemolyticus* beta and treated with Penicillin G, aureomycin, streptomycin or polymyxin D.

were far superior to aureomycin against infection with *K. pneumoniae* type A (47).

Mice were protected by relatively small doses of aureomycin when infected by intracerebral inoculation of lymphogranuloma venereum virus. Guinea pigs survived intraperitoneal infection with many lethal doses of the rickettsiae of Rocky Mountain Spotted Fever, and Epidemic Typhus (50, 51). Treatment of embryonated hens' eggs infected with psittacosis, lymphogranuloma-venereum virus, and the rickettsiae of rickettsialpox, scrub typhus, Q-fever, spotted fever, epidemic and murine typhus was effective. In experiments carried out with epidemic typhus, murine typhus, Q-fever, and psittacosis, it was observed that aureomycin showed little or no direct antirickettsial or virucidal activity. It failed to show any therapeutic activity against many viral infections, such as, influenza, canine distemper, rabies, Newcastle disease, Venezuelan equine en-

cephalomyelitis, poliomyelitis, and mumps (50). When mice were inoculated with a transplanted neoplasm (sarcoma 180) and treated parenterally with 50 mg/kg of aureomycin daily, no effect on the initiation of growth or development of these tumors was observed (16).

Aureomycin was found to be effective for the treatment of relapsing fever in mice and leptospirosis in hamsters. On an equal weight basis, it was more effective than penicillin for these latter infections (52).

Results: In humans, the drug is well tolerated and effective when administered orally. Intramuscular administration has been used for clinical investigation. The antibiotic can be dissolved in 1% procaine solution and 50 mg may be injected in a volume of 2.0 cc of this diluent. Upon repeated dosages, the local sites become erythematous and tender. A dull drawing pain which persists for one-half hour follows these injections (53). More recently a buffered diluent has been prepared containing L-leucine and sodium hydroxide. This diluent may be used *only* for *intravenous administration*. 50.0 mg of aureomycin is dissolved in 2.5 cc of buffer. 200 mg of aureomycin, when dissolved in 10 cc of the buffer, may be slowly injected intravenously several times a day, without untoward reaction. However, care to avoid *extravascular extravasation* is necessary. The indications for parenteral therapy are limited and, as experience with the use of aureomycin is extended, oral administration is found most satisfactory. Comatose patients or children who are severely ill may be given the drug by gavage.

Numerous patients and normal healthy individuals have been given aureomycin orally in doses of 15–100 mg/kg per day for periods as long as seven weeks. Careful hematological, renal, hepatic, and other studies have revealed no evidence of toxicity (53). The only untoward symptoms encountered have been nausea, diarrhea, and vomiting. The incidence of these manifestations has varied with the purity of the different preparations employed. These annoying symptoms are rarely encountered when the individual dose is maintained below 5 mg/kg of body weight. The total daily dosage may be increased by more frequent administration. Some relief of nausea and diarrhea is achieved when an aluminum hydroxide preparation such as creamalin or amphojel is given with the aureomycin capsule (53).

Drug reactions of the allergic or idiosyncratic types, such as drug fever, urticaria, rash, asthma, or mental confusion have not been observed. When doses of 50 mg/kg per day are maintained for a long period of time, emotional symptoms resembling mild depression have been occasionally noted. Two patients have complained of a peculiar feeling of "floating". Neurological examination did not show any abnormality and the symptoms disappeared when the dosage of the antibiotic was reduced or medication discontinued.

Aureomycin is rapidly excreted in the urine and high concentrations can readily be detected (53, 62). With a daily dosage of only 15 to 20 mg/kg of body weight, urinary concentrations of 40 to 80 micrograms of aureomycin per milliliter are attained. This level is sufficient to sterilize the urine of most pathogens. *Proteus vulgaris* and *pseudomonas* organisms are resistant to the action of aureomycin even when higher concentrations are maintained.

A large group of urinary tract infections have been treated with aureomycin (44, 53, 54). We have treated approximately twenty cases of severe, chronic infections due to coli-aerogenes, B. paracolon, and streptococcus fecalis organisms. The cases had not responded to penicillin, streptomycin, or sulfonamide therapy administered either individually or in combination. Many had been ill for several years and associated abnormalities of the urinary tract were

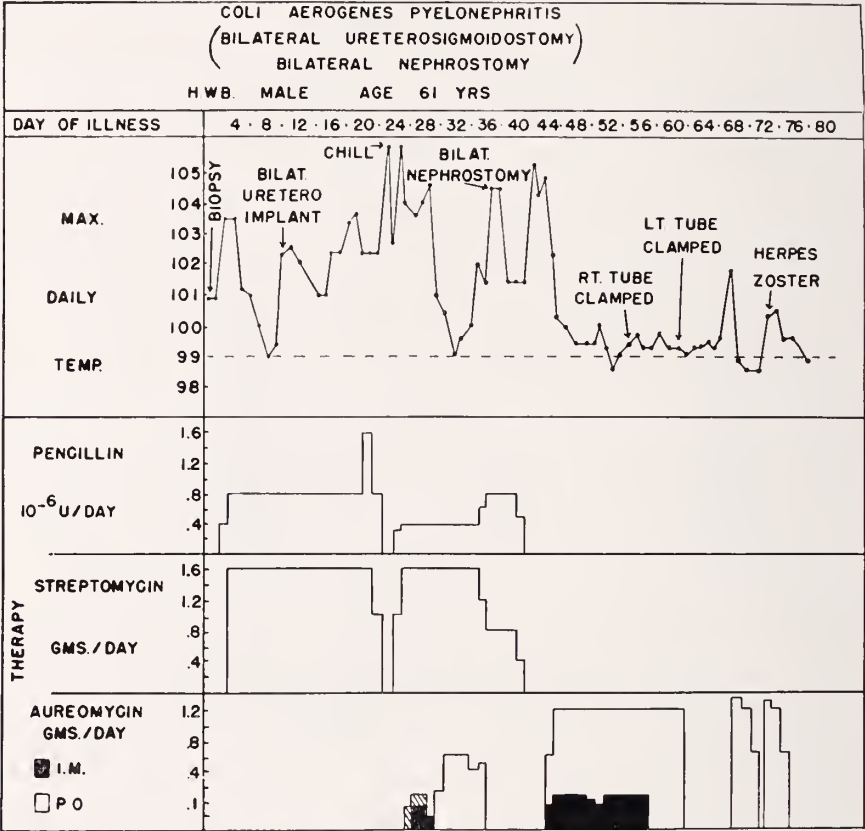


FIG. 13. Coli-aerogenes pyelonephritis in a gravely ill 61 year old male with carcinoma of the bladder, bilateral uretersigmoidostomy and nephrostomy. Response to aureomycin therapy was prompt. At operation, when a bilateral nephrostomy was performed, multiple abscesses in both kidneys were noted. Patient was afebrile and draining into the sigmoid when discharged.

present. These included stricture of the ureter, "cord" bladder, calculus, neoplasm, etc. All cases showed a prompt symptomatic response with defervescence of fever, disappearance of pyuria, and sterilization of the urine. In three cases, proteus infection supervened during or soon after aureomycin therapy. Recurrence of infection was observed in several patients who responded to a second course of treatment. The dosage of aureomycin employed varied with the severity of infection. In the majority of infections, 15-30 mg/kg of body weight each day divided into six equal doses was adequate. In severely

ill patients, 50 mg/kg of body weight have been administered daily for the first few days. Finland and his associates have reported a similar experience in the therapy of urinary tract infections (45, 54).

Five patients with acute or subacute brucellosis, in all of whom positive blood cultures were obtained, have been treated with aureomycin. Four of these patients were infected with *Br. suis* and one with *Br. abortus*. These patients

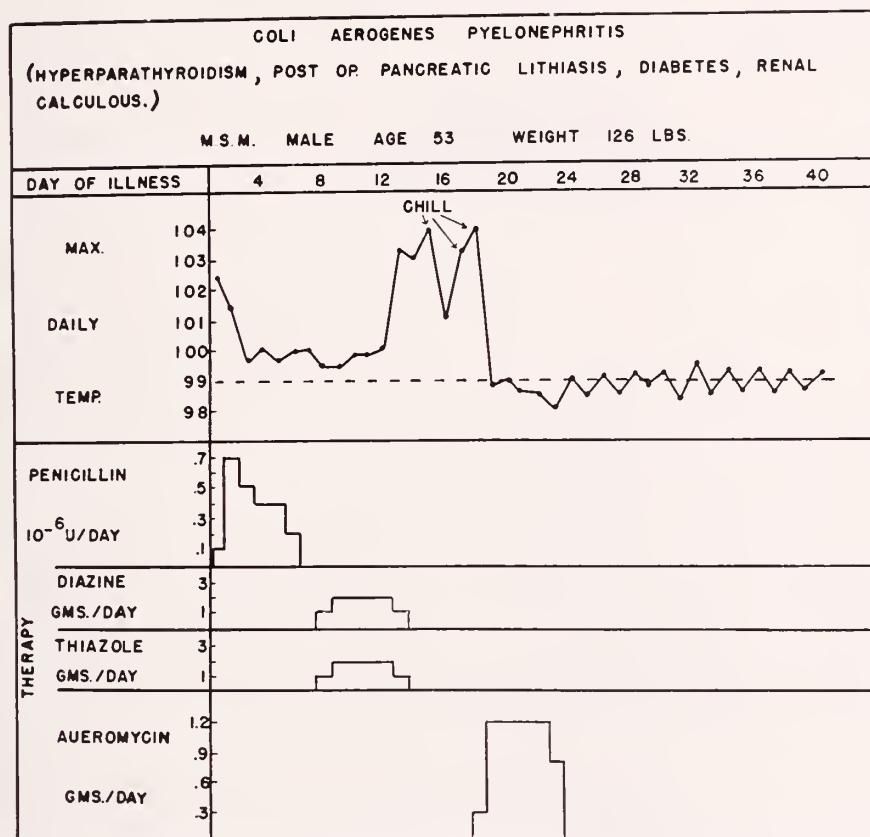


FIG. 14. Coli-aerogenes pyelonephritis in 53 year old male with hyperparathyroidism, pancreatic lithiasis, diabetes, and renal calculus. Urinary tract infection had been present for three years. Prompt remission of fever and pyruia with aureomycin therapy.

had the typical symptomatology of brucella infections and one case was believed to have a brucella endocarditis. The latter patient had not been cured by courses of sulfadiazine, sulfadiazine and streptomycin, or polymyxin. Another patient had not responded to sulfadiazine and streptomycin therapy. All five patients showed a dramatic clinical response to aureomycin. Blood cultures, obtained as early as 24 hrs. after therapy was instituted, were negative. The patients all became afebrile within seventy-two hours with progressive remission of all symptoms and signs. Treatment was continued empirically for approximately two weeks. These patients have been followed for 6 to 11 months without evi-

dence of relapse. All have gained weight and are working at their usual occupation (46). Two additional cases with similar response have recently been treated. Spink has reported successful treatment of brucellosis due to *Br. melitensis* (55). Woodward, et al., have noted the beneficial effect of aureomycin in experimental and human tularemia (80).

On the 6th to 12th day of illness, five cases of typhoid fever were treated with 60 to 100 mg of aureomycin per kg of body weight daily. This oral dose was

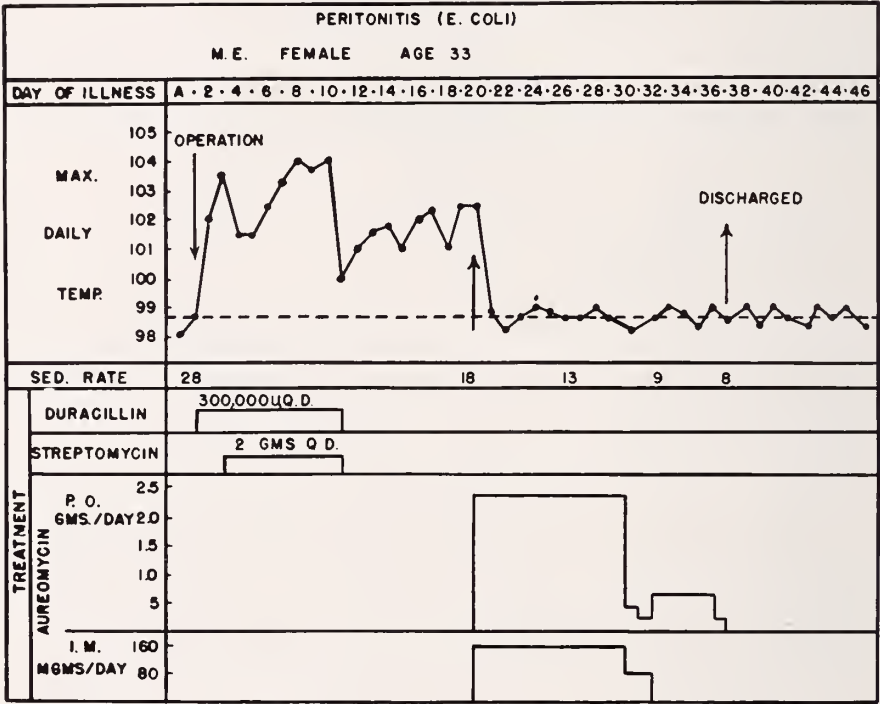
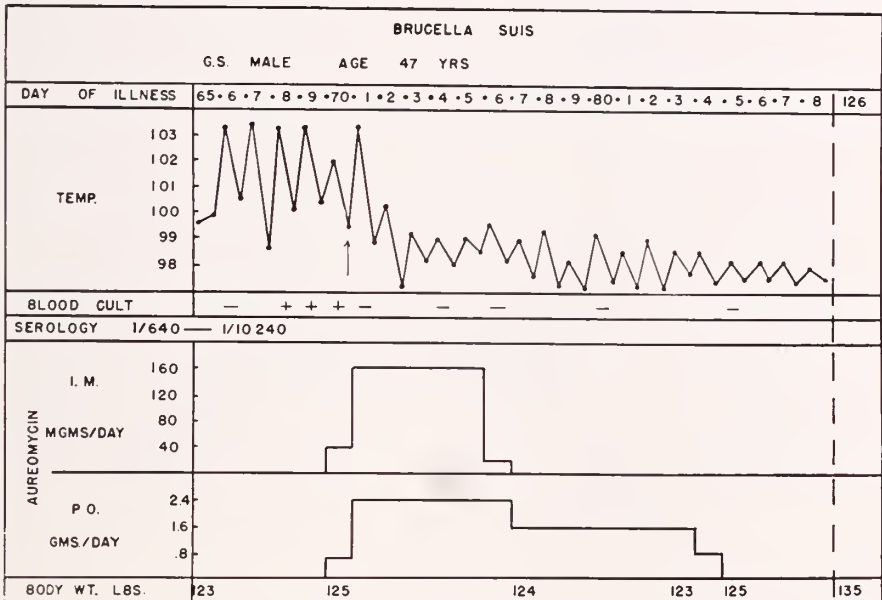
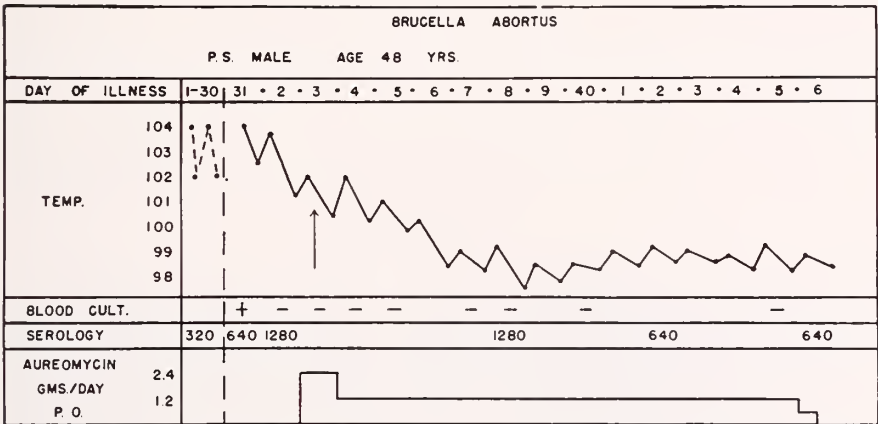
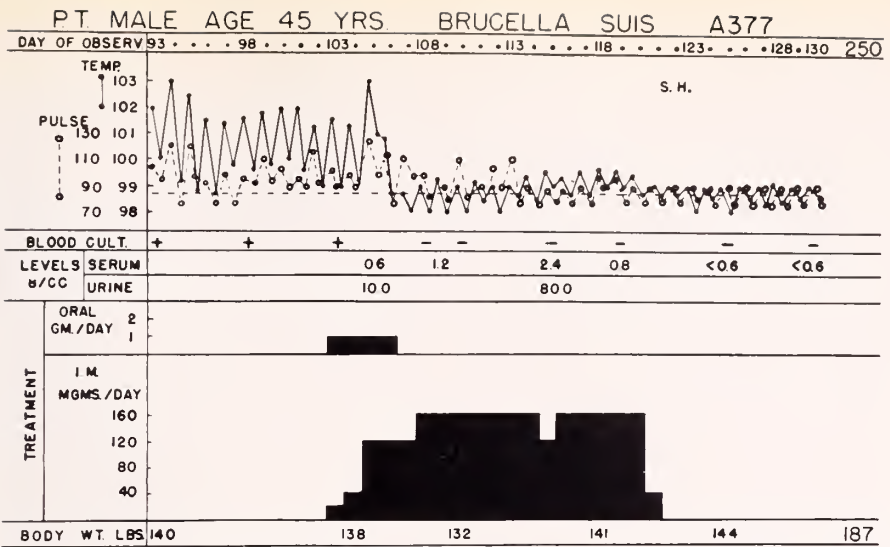
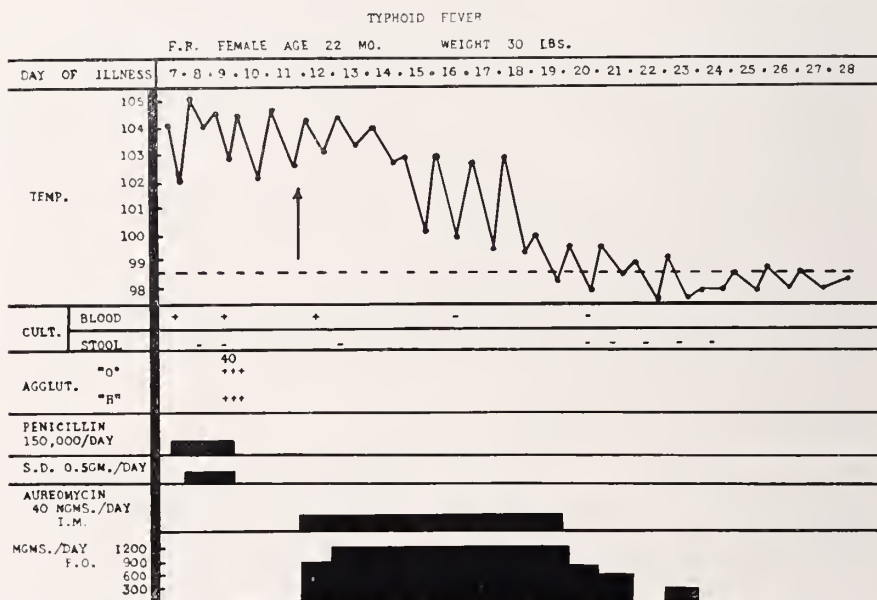
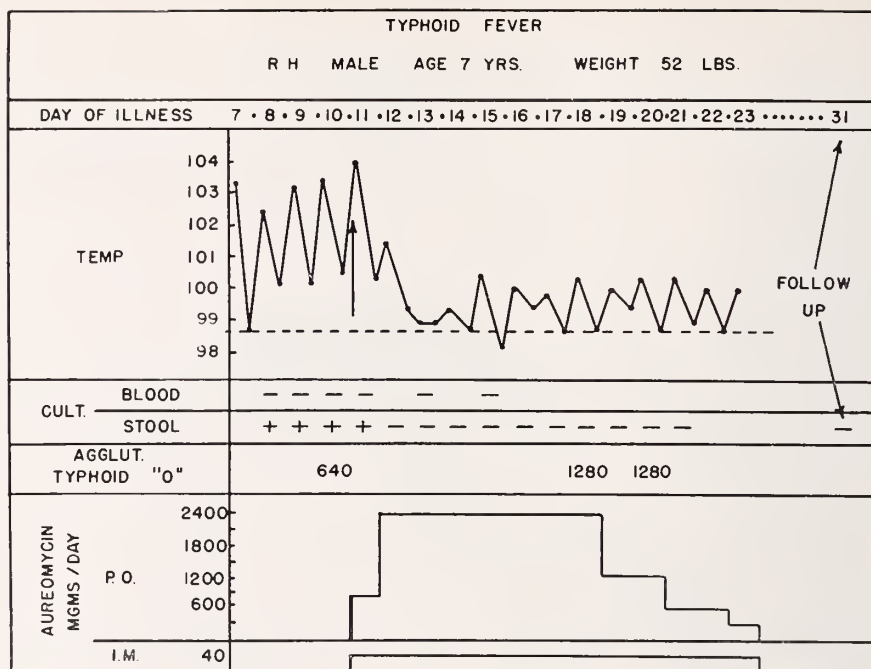


FIG. 15. Peritonitis due to *E. Coli* in a 33 year old female who had sustained rupture of the uterus in child birth. Operative intervention, penicillin and streptomycin therapy were ineffectual. Aureomycin therapy instituted on the 20th day with prompt remission of fever. The patient improved progressively and has completely recovered without further surgical treatment.

supplemented by parenteral administration of 3 to 5 mg of aureomycin per kg. The blood cultures, positive before treatment in 4 cases, promptly became negative. The clinical response, however, was equivocal and defervescence was observed after 24 hrs., 8 days, and 11 days (53). One case relapsed one week after therapy was discontinued. It does not appear that aureomycin is a specific chemotherapeutic agent for typhoid fever. Equivocal results were also noted by Collins, et al., (56), among others, in the therapy of typhoid and salmonella infections with aureomycin. Although the growth of *E. typhosa* is inhibited by aureomycin and chloromycetin at the same concentration 1.25 to 2.5 micrograms



FIGS. 16, 17, 18. Three cases of acute brucellosis treated with aureomycin. None of the cases have relapsed. P. T. had received sulfadiazine, streptomycin and polymyxin during the preceding three months.



FIGS. 19, 20, 21. Three cases of typhoid fever treated with aureomycin illustrating the varied types of response. Note that blood and stool cultures became negative with treatment but the clinical response was variable.

per milliliter, *in vitro*, it would appear that chloromycetin is the more effective therapeutic agent for the treatment of the clinical disease.

TYPHOID FEVER

S G MALE AGE 8 1/2 YRS.

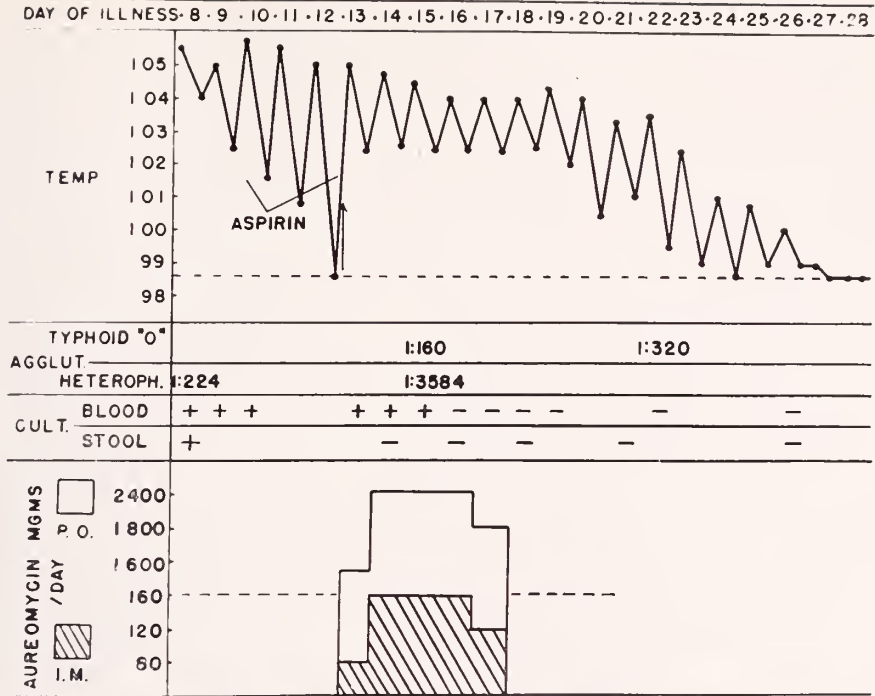


FIG. 21



FIG. 22. 13 year old girl with draining serofulvous sinuses for 5 years. Culture and guinea pig inoculation positive for tubercle bacilli. Drainage ceased ten days after aureomycin therapy was begun. Photograph taken on 9/18/48, one month after beginning treatment. Crusted lesion in left submental region still present at this time.

Six patients suffering from various forms of tuberculosis have been treated. In three, ill with tuberculous meningitis, the drug was ineffective and none of the antibiotic was detected in the spinal fluid (16). A twelve year old Negro female had five scrofulous draining sinuses in her neck for five years. Tubercle bacilli had been cultured and isolated in guinea pigs on numerous occasions and also immediately preceding specific treatment. Administration of aureomycin resulted in closure of all sinuses within 10 days, but therapy was continued for seven weeks. Six months have elapsed since treatment was discontinued without recurrence of the lesions (53). Another patient had been suffering from genito-urinary tuberculosis for two years. One kidney had been removed because of the infection. The bladder, seminal vesicles, and other kidney were involved. Urine examination was repeatedly found to contain tubercle bacilli on culture and guinea pig inoculation and the stained sediment was reported as Gaffky III. Two weeks after aureomycin therapy was begun, culture and animal inoculations were negative for tubercle bacilli and have remained negative to date, six months later. Aureomycin is still being administered in small doses empirically to insure complete eradication. The former patient received 92 grams and the latter patient has already ingested over 100 grams of aureomycin without evidence of untoward reaction or intolerance. A sixth patient with a large tuberculous pulmonary cavity was treated with aureomycin for two weeks without evidence of clinical improvement and a thorocoplasty was then performed. These observations are of interest although the efficacy of aureomycin as a chemotherapeutic agent for tuberculosis cannot be evaluated from this small series of cases.

Eight patients ill with moderate to severe infections produced by the *Staphylococcus aureus* hemolyticus, have been treated with aureomycin. Seven of these patients were new born infants in a nursery and several had pneumonic involvement, one with staphylococcal bacteremia. The eighth patient had repeated positive blood cultures, peritonitis, and phlebitis. A satisfactory prompt response was noted in all patients when aureomycin therapy was instituted. Antecedent therapy with penicillin, sulfadiazine, and, in one patient, streptomycin, had been ineffectual. One infant, whose initial infection was a pyoderma and in whom extensive pulmonary involvement had been present despite continuous penicillin therapy for a period of more than two months, improved rapidly with clearing of the pulmonary infiltration when aureomycin therapy was instituted (57).

Twenty-two patients who by all methods of exclusion have been diagnosed as suffering from primary atypical pneumonia have been treated (58). Cold hemagglutinins were positive in 50% of this series and agglutinins for a strain of streptococcus MG developed to significant titer in 75% of this group. These patients were all severely ill. Treatment with oral aureomycin was followed by prompt defervescence of fever and amelioration of symptoms. In none of these patients was extension of pulmonary involvement noted after therapy with aureomycin was instituted. These observations have been confirmed by other groups of investigators (59, 60). Aureomycin has also been effective in pneumococcal pneumonia (45, 61, 69, 81).

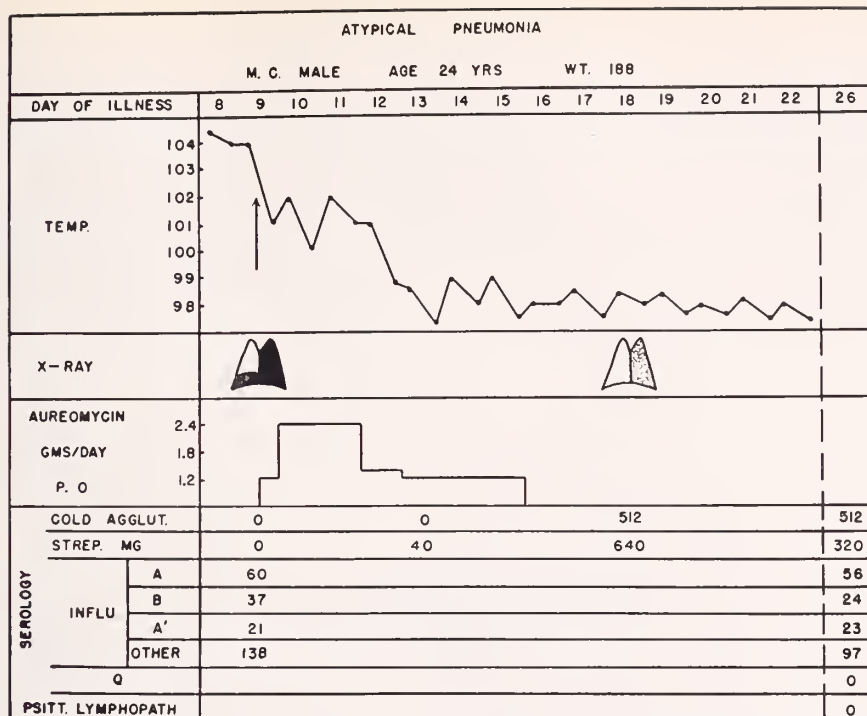


FIG. 23. M. C. was a 24 year old male who was cyanotic and gravely ill. Penicillin and sulfadiazine had been ineffective. Although, he did not become afebrile until 72 hours after aureomycin therapy was begun, he improved clinically within twenty-four hours. This is the longest febrile period noted with aureomycin therapy of atypical pneumonia in this series.

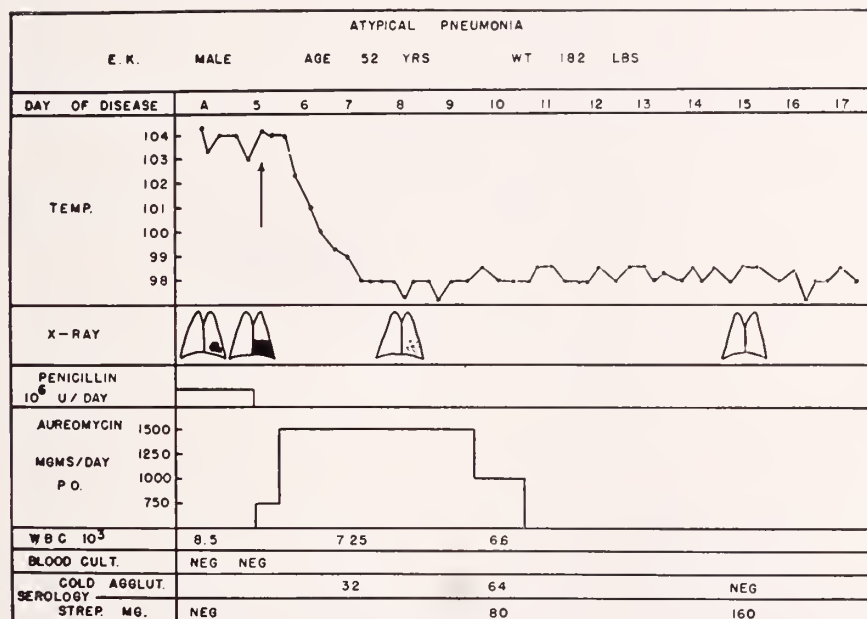


FIG. 24. E. K. a 52 year old male in whom typhoid fever was suspected because of the bradycardia. Penicillin had been ineffective. The patient became afebrile within 36 hours.

A large series of patients suffering from rickettsial infections have been treated with aureomycin (44, 53, 63, 64, 65, 66, 79). The results have been far superior to those observed with PABA and are quite similar to those reported with chloromycetin. Sixteen cases of Rocky Mountain Spotted Fever, eastern type, treated on the third to eighth day of their disease with oral drug became afebrile within an average period of 48 hrs. No complications or deaths were noted among these patients who ranged from 18 months to 50 years in age. The average total period of hospitalization in this group was 8 days (16, 53, 63). Two

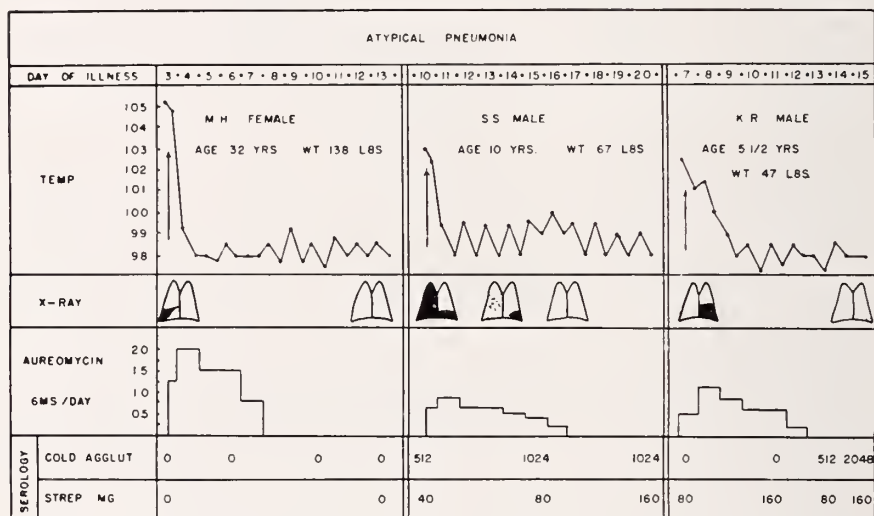


FIG. 25

FIG. 26

FIG. 27

FIG. 25. M. H. treated on the third day of illness. She had received no penicillin or sulfonamide therapy. This patient did not develop cold hemagglutinins or agglutinins for streptococcus, M.G.

FIG. 26. S. S. had been ill for 10 days and previous penicillin and sulfonamide therapy had been ineffective.

FIG. 27. K. R. had been treated for 5 days with sulfadiazine without response.

FIGS. 23, 24, 25, 26, 27. Five cases of primary atypical pneumonia illustrating the response observed with aureomycin therapy. All cases treated had positive x-ray evidence of pneumonia and a relative leukopenia. Serological studies for influenza viruses, Q-fever and other rickettsial diseases, psittacosis and lymphogranuloma venereum were negative.

patients with reerudescant epidemic typhus (Brill's disease) became afebrile within 24 hrs and 48 hrs after therapy was instituted (16, 67). Three cases of Q-fever were treated with excellent results (16). Lenette, et al., have reported successful trial of aureomycin in a more extensive group of infections with the rickettsiae of Q-fever (68). Preliminary results in the treatment of scrub typhus, endemic and epidemic typhus indicate that aureomycin is an effective therapeutic agent (65, 69).

A large group of patients with varied types of infection and disease have been treated with aureomycin. Among these are included an infant ill with meningitis produced by a *Streptococcus fecalis* which was promptly cured with oral and parenteral aureomycin. A child with *D. pneumonia* type 6 meningitis had been

treated with sulfadiazine plus intramuscular and intrathecal penicillin. The infecting organism had become resistant to these latter antibiotics. Recovery was prompt after therapy with aureomycin was instituted (16). Three infants

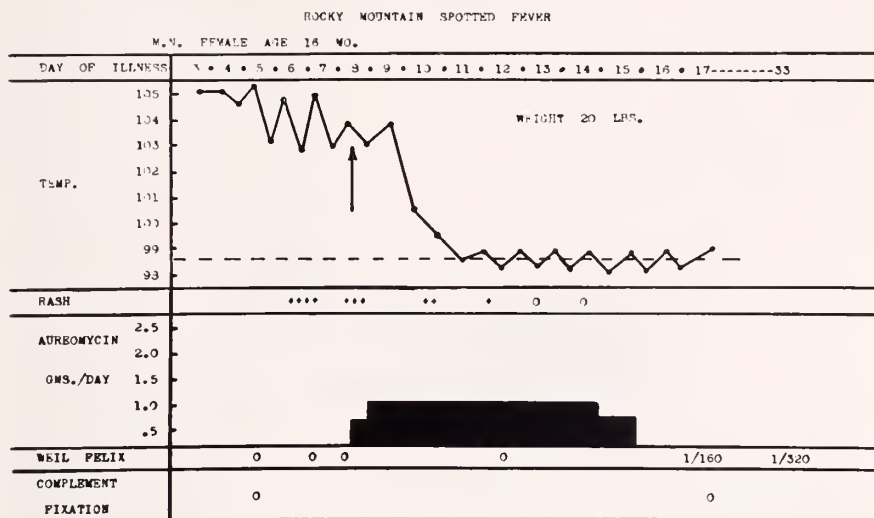


FIG. 28. Rocky Mountain Spotted Fever, Eastern type, treated with aureomycin. 16 month old female treated on the eighth day of disease who became afebrile within 36 hours.

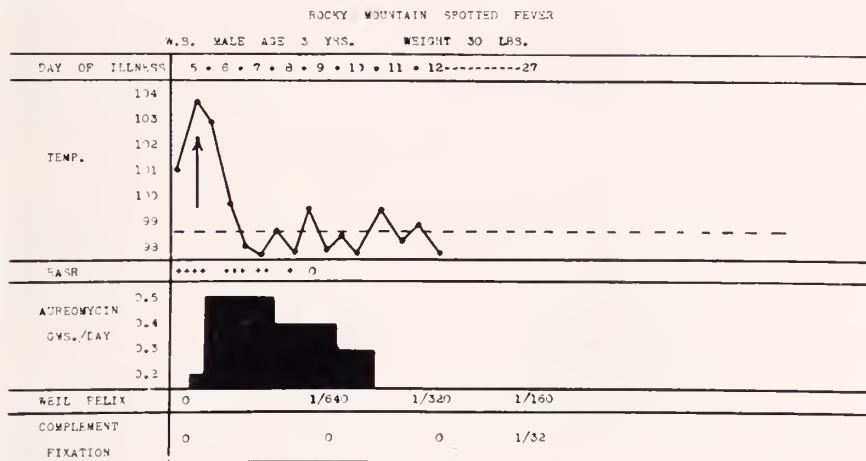


FIG. 29. W. B., 3 year old male treated on the 5th day of disease, who became afebrile within 48 hours.

with meningitis due to H. influenza type B were treated with intravenous and oral aureomycin together with sulfadiazine and both recovered promptly (70).

It is interesting to note that aureomycin has not been detected in the cerebro-spinal fluid when parenterally or orally administered. This has been true in normal patients as well as in 3 cases of tuberculous meningitis. In the cases of acute purulent meningitis, detectable levels were noted during the height of the

disease. The drug disappeared from the spinal fluid as the inflammation subsided even though the administration of drug was maintained (16).

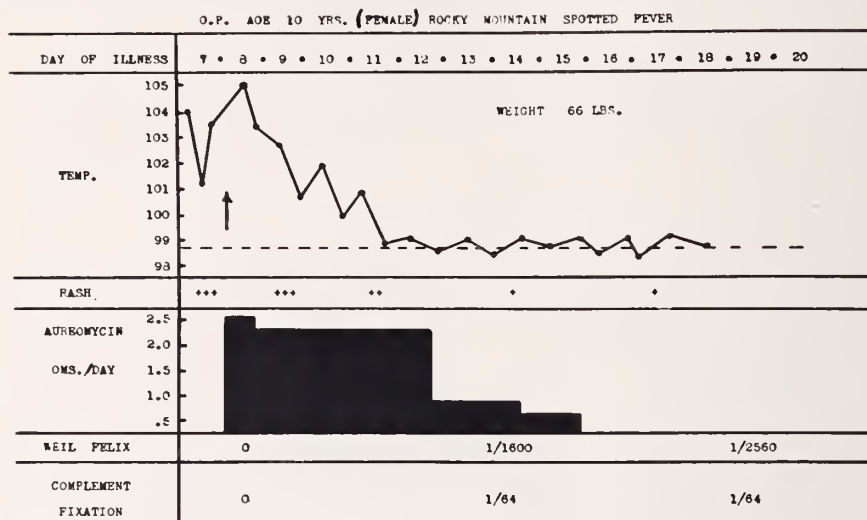


FIG. 30. G. P. 10 year old female treated on the 8th day of disease who became afebrile within 72 hours.

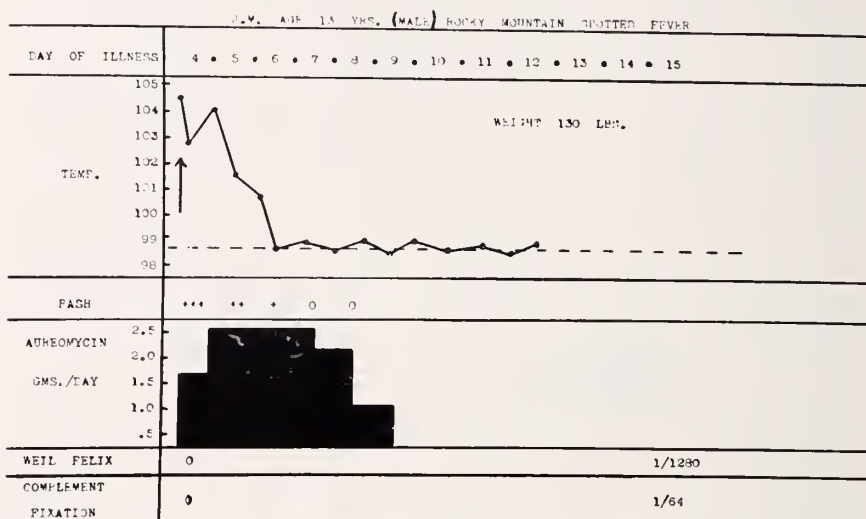


FIG. 31. J. M. 13 year old boy treated on the fourth day of his illness who became afebrile within 48 hours.

Two cases of subacute bacterial endocarditis have been treated. Both had numerous positive blood cultures before treatment. One case infected with a strain of streptococcus fecalis cleared completely soon after aureomycin therapy was begun and has remained well for seven months. The other, who also had congenital heart disease, appeared to respond and remained afebrile for five

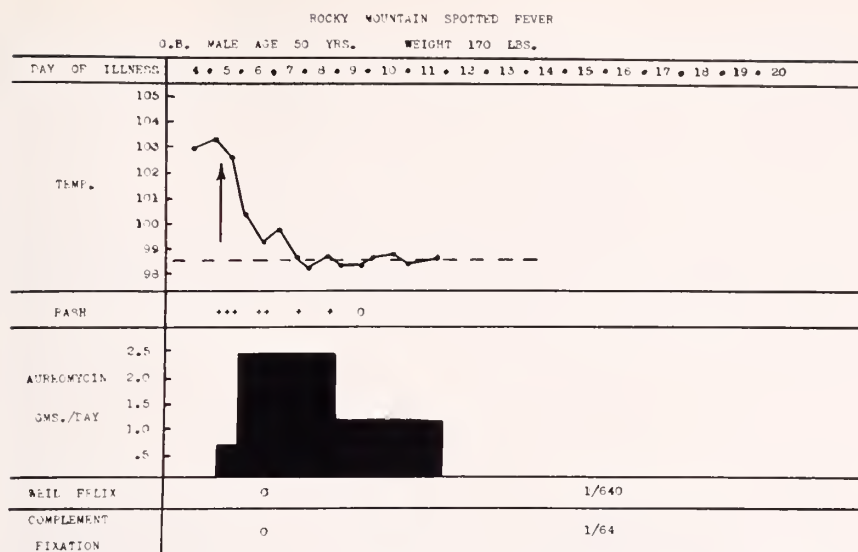


FIG. 32. G. B. 50 year old male treated on the 5th day of disease who became afebrile within 48 hours.

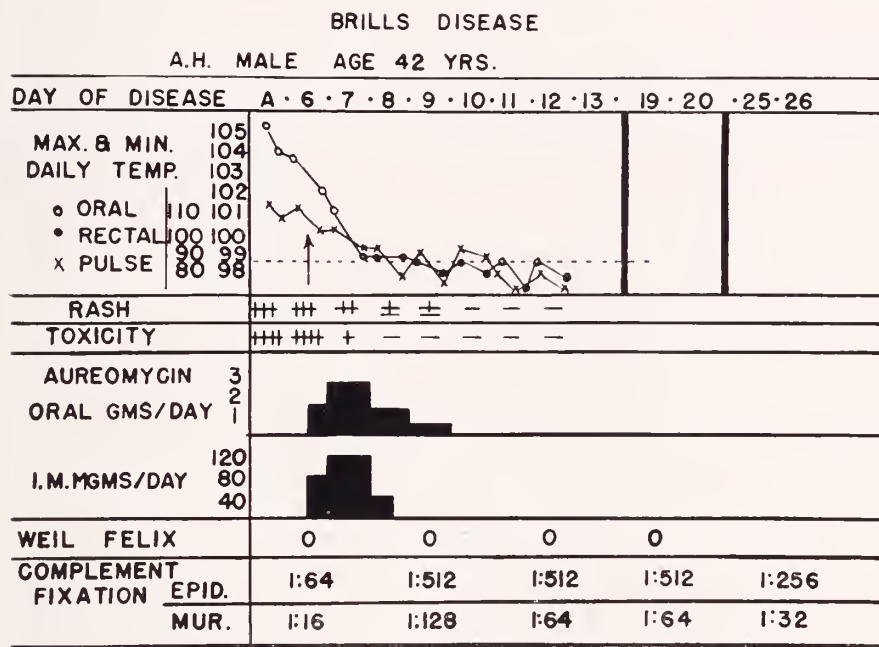


FIG. 33. A. H. Recrudescent epidemic typhus (Brill's disease). The patient was treated with aureomycin on the sixth day of his illness. He became afebrile and asymptomatic within 36 hours.

weeks while receiving aureomycin. When treatment was discontinued, cultures promptly became positive and sterilization was not achieved after treatment with

aureomycin was reinstituted even though intravenous therapy was increased to 10 mg/kg daily in addition to 50 mg/kg orally. The *in vitro* resistance of this organism (*strep. salivarius*) was unchanged and remained in the susceptible range (1.0 to 2.0 micrograms per milliliter). Penicillin therapy in this latter patient has been unsuccessful.

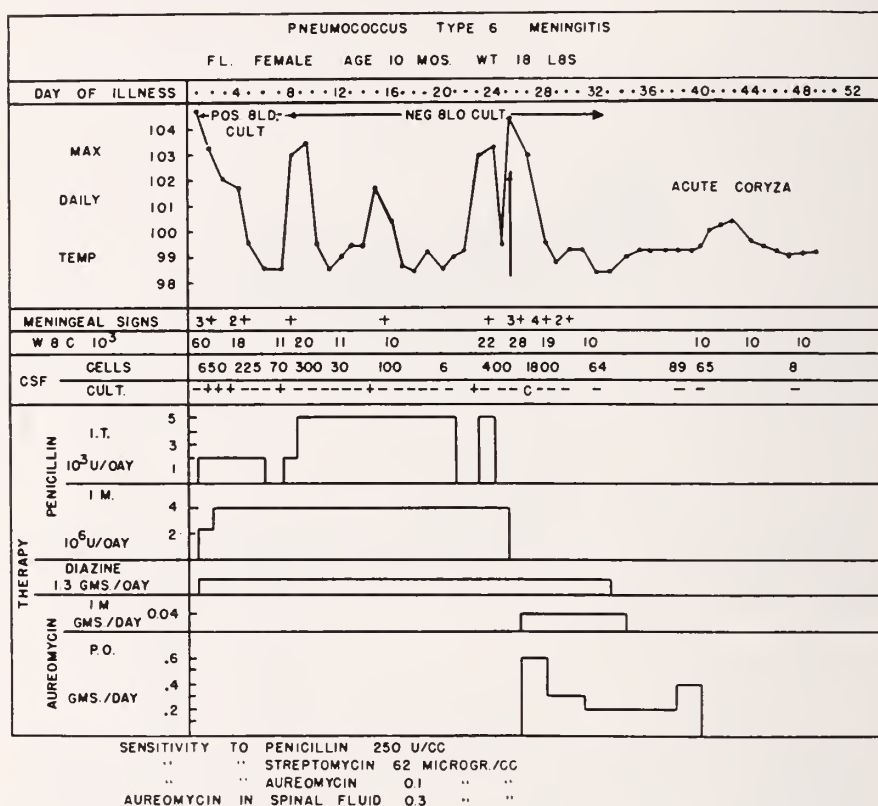


FIG. 34. F. L. aged 10 months with pneumococcus type 6 meningitis. Sulfadiazine and penicillin therapy for three weeks only partially effective. Aureomycin begun on the 25th day with prompt defervescence and recovery without sequelae. Note that aureomycin was present in the spinal fluid during the inflammatory phase.

Two infants with postoperative meningitis secondary to drainage of brain abscesses, one due to a staphylococcus aureus and the other to *E. coli*, were cured with aureomycin. Two patients with peritonitis and two with localized postoperative peritoneal infections have shown prompt remission of signs and symptoms following aureomycin therapy. *E. coli* and streptococcus fecalis were the offending organisms (16).

One patient ill with polioencephalitis, one with noma, and one with pancreatic necrosis, secondarily infected, have been treated with aureomycin without beneficial results. Two cases of whooping cough and four patients ill with erythema multiforme did not appear to have the course of their illness materially

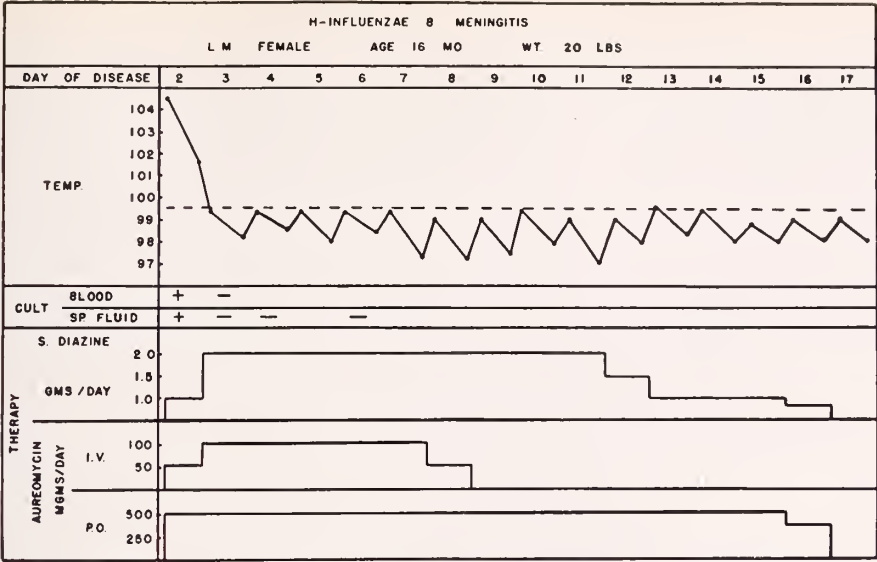


FIG. 35. L. M. aged 16 months with H. influenza B meningitis. Treatment with sulfadiazine and aureomycin was followed by prompt uncomplicated recovery. (Courtesy of Dr. C. A. Chandler)

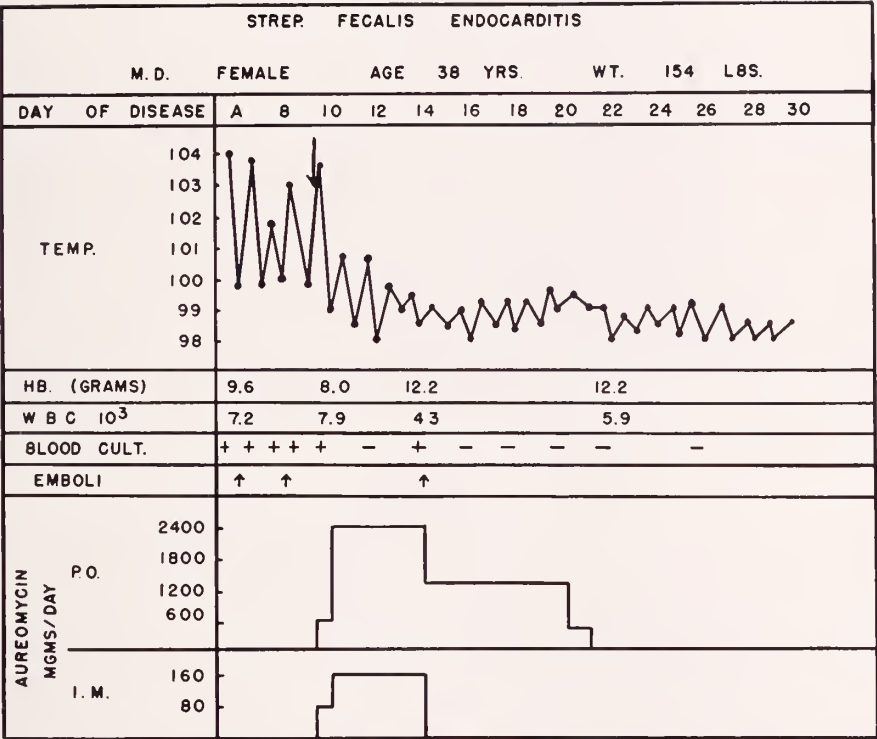


FIG. 36. Subacute bacterial endocarditis due to the streptococcus fecalis in a 38 year old female. Treatment with penicillin at home had induced a temporary clinical remission. Aureomycin treatment was begun on the tenth day following relapse. She has remained well to date.

affected by aureomycin therapy. Eleven cases of measles have been treated early in their disease. The results were erratic and one cannot determine whether aureomycin influenced the progress of the illness. Mumps and herpes zoster have appeared in patients receiving aureomycin for other infections (16).

Various investigators have reported excellent results with aureomycin in the treatment of lymphogranuloma venereum and granuloma inguinale (54, 71, 72, 73, 74). Preliminary reports on the treatment of psittacosis with aureomycin are favorable (69). The treatment of early syphilitic primary lesions in experimental animals and man has resulted in healing and the disappearance of spirochetes (69, 75, 76). Preliminary observations indicate that clinical improvement of patients suffering from amebic dysentery, with elimination of *E. histolytica*, may occur following oral administration of aureomycin (85).

A preliminary report on the use of aureomycin for the treatment of gonococcal urethritis was favorable although the response was not quite as dramatic as that observed with a single dose of 300,000 units of slowly absorbed penicillin (45).

Aureomycin borate was found to be non-irritating to the inflamed conjunctiva in 0.5 to 1.0% solution. Treatment of ocular inflammation was apparently beneficial in the pyogenic infections and possibly in certain infections usually considered of virus etiology (77, 78).

Comment. It is evident that aureomycin is a valuable addition to the chemotherapeutic armamentarium. Early clinical trial has not delimited the complete spectrum of its usefulness. To date, serious infections caused by numerous gram-positive and gram-negative bacilli, rickettsiae, and viruses of the lymphogranuloma group have been shown to be definitely ameliorated. The optimal oral dosage of aureomycin has not been determined. At present, 5 mg/kg of body weight administered six to twelve times a day is recommended. This may soon be changed as less nauseating preparations become available, so that larger amounts may be given at less frequent intervals.

Parenteral preparations of aureomycin soon may be released for general use. They will be of distinct advantage in severely ill patients in whom rapid saturation is necessary or under circumstances when the patients' condition does not permit ingestion of the antibiotic.

CONCLUSIONS

The studies with these antibiotics have been quite interesting from their biological implications. Unfortunately, study of their mechanism of action has been curtailed because of the rapid clinical application.

The polymyxins are effective antibiotics for infections caused by certain gram-negative micro-organisms but, because of their toxicity they do not fulfill the criteria demanded of a chemotherapeutic agent.

Chloromycetin has been effective in experimental and clinical infections produced by many gram-negative micro-organisms, rickettsial, and certain viral agents. The response observed in the treatment of the rickettsial diseases, typhoid fever, brucellosis, and *Pseudomonas aeruginosa* urinary tract infections has been outstanding.

Aureomycin has been successfully employed in the treatment of rickettsial infections, primary atypical pneumonia, brucellosis, severe staphylococcal infections, urinary tract infections with *E. coli*, *A. aerogenes*, and *Streptococcus fecalis*, pneumococcal and streptococcal infections. The immediate response of infections with the lymphogranuloma-ornithosis group of viruses has been promising.

The toxicity of chloromycetin and aureomycin has been minimal. The reactions observed have been annoying rather than serious. Their clinical application will probably expand rapidly as investigations are completed.

With the advent of aureomycin and chloromycetin, many infections once considered among the dreaded plagues of mankind may, in the words of Dr. Hans Zinsser, "be confined, like other savage creatures, in the zoological gardens of controlled diseases".

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THE MODE OF ACTION OF PENICILLIN IN RELATION TO ITS THERAPEUTIC USE*

HARRY EAGLE, M.D.**

Bethesda, Md.

The therapeutic action of penicillin is determined in large part by the aggregate time for which the drug remains at effective concentrations at the foci of infection. The absolute concentration is of little significance provided only that it is in excess of that necessary to kill the particular bacterial strain at the maximal rate. Increasing the penicillin concentration beyond that optimally effective level does not further accelerate the rate of death of the organisms, either *in vitro* or *in vivo*.

The aggregate time for which penicillin remains at bacterial levels is not, however, the only factor which determines its therapeutic activity. In the first place, when bacteria are being acted on by penicillin, while some of the organisms are dying, the relatively resistant organisms are not multiplying, so that the progress of the infection is halted. Further, the bacteria damaged but not yet killed by penicillin become susceptible to the normal defense mechanisms of the body. In consequence, the rate of bactericidal action *in vivo* is a composite of the direct effect of the drug itself, plus the effect of the body's own defense mechanisms on the penicillin-damaged organisms. Then again, even after the drug has disappeared from the body fluids, the organisms do not immediately resume multiplication. Instead, there follows a period of some two to four hours before the bacteria can recover sufficiently from the toxic effects of the drug to resume multiplication. During this time they are relatively avirulent and remain susceptible to the body's defense mechanisms. Only after the bacteria have recovered from the toxic effects of the drug do they resume multiplications, and regain their normal resistance to the host.

It follows that the total duration of penicillin action is the sum of the time for which it remains at effective levels at the foci of infection, plus the time required for the bacteria to recover from its toxic effects and resume multiplication. Even then, if only a relatively small number of organisms have survived the previous treatment, they may re-multiply for several generations without significantly increasing the total number of bacteria, and adversely affecting the efficacy of treatment. Under such circumstances, doses of aqueous penicillin which provide effective levels in the tissues for only 3 to 4 hours may be safely repeated at 8-hour intervals.

*From the National Institute of Health, Public Health Service, Federal Security Agency, Bethesda, Md.

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GENERALIZED BLOOD PLATELET THROMBOSIS

REPORT OF THREE CASES WITH NECROPSY FINDINGS*

MARTIN A. GREEN, M.D. AND SEYMOUR ROSENTHAL, M.D.

Thrombocytopenic purpura associated with generalized blood platelet thrombosis of small blood vessels was first described by Moschcowitz (1). Recently its clinical and pathological features were reviewed by Fitzgerald, Auerbach and Frame (2) who suggested the name *thrombocytic acroangiothrombosis* and by Singer, Bornstein and Wile (3) who offered the name *thrombotic thrombocytopenic purpura* for this disease.

Fifteen cases have been recorded (1 to 10), all from post mortem studies. The central nervous system was available for post mortem examination in only nine instances. In a very recent article Adams, Cammermeyer and Fitzgerald (11) reviewed the neuropathologic aspects of the disease. Since neurological manifestations are almost always present and are often prominent, it is felt that a report of three additional cases in which histological studies of the nervous system were carried out will be of interest.

Clinical features summarized. The disease is encountered most frequently in the younger decades of life and predominantly in females. It is usually preceded by an upper respiratory infection. The onset is usually marked by some of the following symptoms: malaise, generalized aches and pains, arthralgia, throbbing headaches, nausea, vomiting and a fluctuating low grade fever. These accompany the symptoms characteristic of any of the thrombocytopenic purpuras, such as petechiae and ecchymoses, melena, hematuria and pallor. Manifest or latent jaundice is commonly present. In the course of the illness central nervous system symptoms appear, either in the form of mental changes or in the character of focal involvement. The former may include confusion, restlessness, delirium, stupor, or coma; the latter is manifested most frequently by cranial nerve palsies, hemiplegia and aphasia. There is no constant pattern of neurological signs but characteristically they are transitory in nature and tend to wax and wane during the progress of the illness.

Laboratory studies disclose a diminished number of platelets, prolonged bleeding time, positive tourniquet test, normal clotting time and poor clot retraction, findings which are common to all the thrombocytopenic purpuras. In addition, however, there is an accompanying hemolytic anemia, often severe in character. The bone marrow shows a normal or slightly increased number of megakaryocytes with normal platelet formation. The cerebrospinal fluid was normal in those cases in which it was examined.

The disease is brief in its course and usually terminates fatally within one to eight weeks. In one case there was transitory improvement for several weeks, death occurring three months after onset of the illness. Splenectomy performed in two instances had no beneficial effect.

* From the Laboratories of The Mount Sinai Hospital, Division of Neuropathology and General Pathology, New York.

CASE REPORTS

Case 1. History. (Adm. #564477, P.M. #13692) The patient, a white male aged 69 years, entered the Mount Sinai Hospital on May 10, 1947. Except for several episodes of recurrent pneumonia (the last attack three years previously), the patient was apparently well until the onset of his present illness. One week before the first symptoms were noted he was vaccinated against smallpox. His illness began two weeks prior to admission, with chills, cough and fever which subsided after three days. One week before admission, following an attack of "dizziness," he began to complain of severe headaches, disagreeable nauseating odors, anorexia, a cough productive of gradually increasing amounts of bloody sputum, left chest pain and weakness, all of which were present on admission. One day before entering the hospital, he began to display mental changes. He wept frequently, had difficulty in finding words, repeated some words and phrases and certain motions aimlessly, misused objects, and was slow in carrying out commands. His level of awareness fluctuated, and at times he was brighter, more cooperative and more capable.

Examination. The temperature was 101.2°F., pulse 100 and respirations 24. The patient appeared weak, pale and showed other evidence of chronic illness.

Scattered purpuric spots were present on both legs and the left arm. The trachea was deviated to the right. The chest was emphysematous and the lungs hyperresonant. A few moist rales were present at both bases. Cardiac percussion was unsatisfactory because of the emphysematous chest, and the point of maximum impulse could not be felt. Heart sounds were distant and no murmurs were heard. Blood pressure was 140 systolic and 90 diastolic. The liver and spleen were not palpable. The prostate was diffusely enlarged but was neither nodular nor hard. Peripheral arterial pulsations were vigorous. There was no lymph node enlargement.

Neurological examination revealed an aphasia of the mixed type. There was a drift of the right upper extremity and the right biceps reflex was greater than the left. There was a suggestive right visual field defect but this was not confirmed.

Laboratory data. On admission, the blood count revealed hemoglobin, 78 per cent; red blood cells, 4,020,000; white blood cells, 8,650 with a differential of segmented polys, 71 per cent; nonsegmented polys, 1 per cent; lymphocytes, 20 per cent; monocytes, 6 per cent; and eosinophiles, 2 per cent. A blood count repeated four days later showed hemoglobin, 61 per cent; red blood cells, 3,430,000; white blood cells, 8,900 with segmented polys, 59 per cent; non-segmented polys, 5 per cent; lymphocytes, 22 per cent; monocytes, 14 per cent; reticulocytes, 0.5 per cent; hematocrit, 31 per cent; and platelets, 70,000. The urine showed a specific gravity of 1.020, a trace of albumin, 4 to 6 white blood cells and 8 to 10 red blood cells per high power field with rare granular casts. Blood Kahn was negative. Tourniquet test was negative.

Sternal aspiration disclosed hyperactive marrow affecting particularly the myeloid elements. Megakaryocytes were present in normal numbers and showed platelet formation.

Chest x-ray showed exaggeration of the markings at the right base and slight cardiac enlargement. X-ray of the skull was negative. Electroencephalography suggested a rapidly growing neoplasm in the left temporal region extending to the inferior parts of the left frontal and parietal lobes.

Lumbar puncture yielded clear but mildly xanthochromic cerebrospinal fluid under normal pressure. Pandy was 4 plus; total protein was 54 mg. per cent. There were 2 red blood cells per cubic mm. The Wassermann and colloidal gold reactions were negative.

Course. The first diagnostic possibilities considered were, 1) bronchogenic carcinoma with cerebral metastases, 2) thrombocytopenic purpura with pulmonary and cerebral bleeding, and 3) bronchiectasis with secondary suppuration and metastatic brain abscess.

On the third day in the hospital the patient's condition appeared to decline rapidly. He was alternately restless, confused, irrational, unresponsive and hyperirritable. The petechial and purpuric lesions became more numerous. Incontinence of urine and feces

developed. Chest pain, headache and hemoptysis of mixed old and fresh blood persisted. No new neurological findings were noted. He died one week after admission, three weeks after the onset of the illness.

Throughout the stay in the hospital, the patient ran a low grade fever ranging between 99° and 101°F., rising to 103.2°F. on the day of death. Treatment consisted of intramuscular penicillin and blood transfusions.

General necropsy findings. *Gross.* Petechiae and purpura were scattered over the entire body, with some also present over the parietal pleura and diaphragm.

The *heart* was firm and an adhesive pericarditis was present over its right side. There were no pericardial or epicardial petechiae. A 4 mm. purpuric area was present in the endocardium of the right auricle. The sectioned myocardium of the left ventricle contained a few scattered petechiae.

The *lungs* showed marked bullous emphysema of all lobes. Other than a hemorrhagic emphysematous bleb in the right lower lobe there was no evidence of pleural or parenchymal hemorrhage.

The *liver* was flabby, fatty and congested. The *spleen* was very soft and the sectioned surface was a deep reddish-purple, with diffuent pulp.

The *kidneys* were normal in size and shape. The capsules stripped with moderate difficulty, revealing numerous small, depressed cortical scars, but no petechiae. There were no hemorrhages in the calyces, pelves or ureters. A few petechiae were present in the bladder. A 1.5 x 2 cm. yellow nodule was present in the left *adrenal* cortex which also contained a few scattered petechiae.

The mucosa of the *stomach*, *distal ileum* and *rectosigmoid* was flecked with petechiae and the lumina in these regions contained reddish-brown and bright red blood.

The lumbar *vertebral bone marrow* was red and abundant. The trabecular structures were normal.

*Microscopic observations.** The *myocardium* contained many small thrombi in the arterioles and capillaries. There was interstitial and mild perivascular fibrosis. The right ventricle was the site of an old fibrous pericarditis with foci of chronic inflammatory cells. There were small focal hemorrhages in the subpericardial fat.

The *lungs* were intensely congested and hemorrhagic and the alveoli markedly distended. No thrombi or megakaryocytes were seen.

In the *liver*, in addition to extensive fatty vacuolization and severe hyperemia, there were thrombi in the small vessels in subcapsular and portal areas. The *spleen* was intensely congested. Many organizing thrombi were present in the small arterioles.

The *renal* capsule was thickened with many adherent, shaggy, fibrovascular tags, and many small cortical scars were seen. Multiple platelet thrombi in various stages of organization were present in the terminal arterioles and capillaries in the cortex and medulla. Many of these were in either the afferent arterioles before it subdivided within the glomerulus or within the capillary loops of the glomerular tufts. Thrombi were also present throughout the *pancreas* (including the islets), in the *adrenals*, *lymph nodes* and *intestine*.

Skin. At the vaccination site there was denudation of squamous epithelium with surface hemorrhage. Several cells of the adjacent epithelium contained intranuclear inclusion bodies. Several organizing platelet thrombi were present in the capillaries. There were foci of chronic inflammatory cells in the corium.

The *vertebral marrow* was hyperplastic with an increased number of megakaryocytes and an occasional focus of hemorrhage. A rare capillary thrombus was present.

Central nervous system. *Gross.* The brain was essentially normal except for two pete-

* The following stains were employed: hematoxylin and eosin, phosphotungstic acid hematoxylin, Weigert's fibrin stain, benzidine stain, Turnbull blue for hemosiderin, and the Giemsa stain. In addition to these stains, sections of the central nervous system were stained by the Nissl, Weil and Cajal (Globus modification) gold sublimate methods.

chial hemorrhages in the posterior portion of the right inferior frontal convolution and advanced arteriosclerosis of the blood vessels at the base of the brain.

Microscopic observations. Sections of the cerebral cortex disclosed a generalized paucity of nerve cells and a generalized gliosis. The cortical cytoarchitecture was poorly preserved. A conspicuous alteration was the presence of thrombi in numerous small blood vessels. The thrombi either partially or completely occluded the vascular lumens. Frequently the endothelial cells of such thrombosed vessels were swollen and proliferated into and around the thrombi. A small number of these vessels did not exhibit the endothelial changes. The parenchyma in the vicinity of the affected vessels showed no significant alterations. Occasionally there were small collections of red blood cells in the perivascular spaces of the thrombosed vessels. Several small hemorrhages were encountered about either congested, non-thrombosed blood vessels or blood vessels undergoing necrosis. Many of the smaller arteries exhibited arteriosclerotic changes.

The cerebral subcortex showed a generalized increase of oligodendroglia. No thrombosed blood vessels or hemorrhages were seen. There was a single small area of softening, situated largely in the subcortex but extending into the cortex as well. No thrombotic lesions or hemorrhages were seen within this area or in the surrounding tissue.

Sections of the midbrain showed a small number of thrombosed blood vessels. There were no hemorrhages or areas of rarefaction.

Sections of the medulla disclosed no thrombotic or other lesions.

The thrombi. The following description of the vascular lesions applies to all the cases herein reported. The thrombi were found in the terminal arterioles and capillaries in several stages of formation and organization within the same organ. In one type of lesion, as seen in an hematoxylin and eosin preparation, there was a loose aggregation of numerous small, distinct, eosinophilic granular bodies which were slightly refractile when viewed under reduced light. The endothelium of the blood vessels containing these thrombi appeared normal. These lesions probably represented a fresh precipitation of platelets and were, therefore, "young" thrombi (fig. 1a). Other thrombi appeared as agglutinated, eosinophilic, granular masses, completely or partially occluding tremendously dilated vascular lumens. The blood vessels containing these thrombi frequently showed endothelial proliferation, with invasion of the thrombotic mass by cells resembling young fibroblasts. These thrombotic vessels were probably older lesions (figs. 1b and 2). In some thrombi, small amounts of fibrin, in the form of fine needles or thick strands, were demonstrated by Weigert's fibrin stain and the phosphotungstic acid hematoxylin stain. The benzidine stain revealed that the thrombi were not composed of red blood cells or products of their degeneration.

Case 2. History.* (Adm. #495216, P.M. #12277) The patient, a white female, aged 33 years, entered the Mount Sinai Hospital on September 15, 1942. Approximately two weeks prior to admission, radiotherapy had been applied to her right hand for a dermatitis caused by adhesive tape. Five days later she noted generalized weakness, which became progressive, and with it there developed throbbing headaches, noted especially on walking. Pallor, anorexia, and ecchymoses were noted a few days before admission.

Her previous history was negative. Both parents were diabetics and her father died at 71 years of age of a cerebral hemorrhage. A brother died of periarteritis nodosa.

Examination. The temperature was 100.4°F., pulse 24 and respirations 22. There was marked pallor. Petechiae and fading ecchymoses were present on the trunk and extremities. There was a lid lag, the thyroid was slightly enlarged, and a fine tremor of the hands was present. The heart and lungs appeared normal. The blood pressure was 100 systolic and 70 diastolic. The liver and spleen were not palpable. Small axillary lymph glands were present bilaterally. There were no neurological findings.

Laboratory data. Hemoglobin, 38 per cent; red blood cells, 2,000,000; white blood cells, 9,900 with 45 per cent segmented and 13 per cent non-segmented polys, 1 per cent monocytes,

* This case was previously reported by Bernheim (7).

1 per cent basophiles, 1 per cent eosinophiles, and 29 per cent lymphocytes. Some of the latter cells may have been micromyeloblasts. There were 4 myelocytes, 3 normoblasts and 2 erythroblasts per 100 white blood cells. Platelets were markedly reduced. The

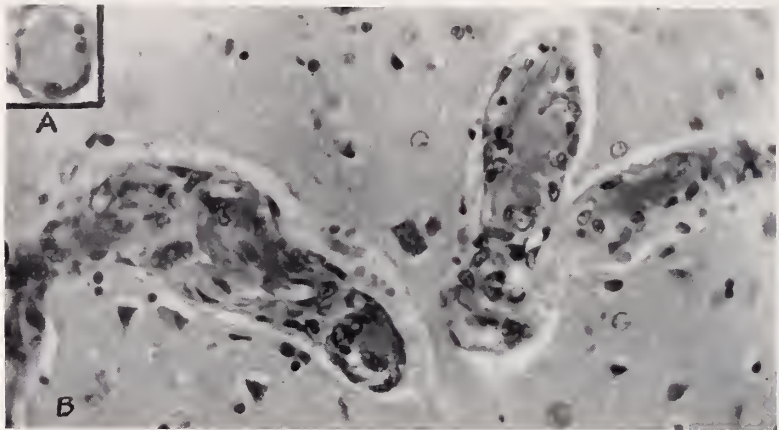


FIG. 1a. Thrombotic blood vessel of cerebral cortex without endothelial proliferation. (Hematoxylin and eosin stain; $\times 250$).

FIG. 1b. Blood vessel of cerebral cortex containing thrombus and exhibiting marked endothelial proliferation. (Hematoxylin and eosin stain; $\times 250$).

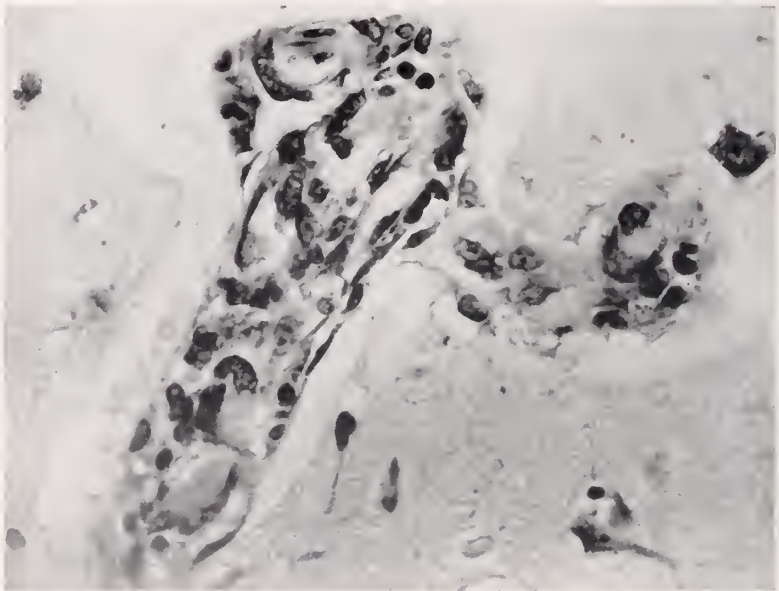


FIG. 2. Thrombotic blood vessel of cerebral cortex with endothelial proliferation. (Nissl stain; $\times 600$).

tourniquet test was positive. The day after admission the sedimentation time was found to be 30 minutes; bleeding time, more than 30 minutes; clotting time, 20 minutes. There was no clot retraction after 48 hours. That day the hemoglobin was 30 per cent; red blood cells, 1,650,000; white blood cells, 11,000 with 45 per cent segmented and 12 per cent non-

segmented polys, 8 per cent eosinophiles, 2 per cent basophiles, 17 per cent lymphocytes, 1 per cent monocytes 2 per cent myeloblasts, 8 per cent myelocytes, 6 per cent reticuloocytes and 5 per cent normoblasts. The blood urea nitrogen was 18 mg. per cent; sugar, 90 mg. per cent; cholesterol 260 mg. per cent, with esters 140 mg. per cent; icterus index 8; albumin, 3.6 and globulin, 2.0 Gm.; Wassermann reaction was negative. A bone marrow aspiration revealed a slightly hyperplastic marrow with a normal cell distribution. The urine showed 1 plus albumin, no bile, 1:10 urobilin, 3 to 4 red blood cells and 1 to 2 white blood cells per high power field.

Course. On the day after admission, following the bone marrow aspiration, the patient developed signs of shock. She was given intravenous infusions and was transfused. Neurological examination revealed a semi-comatose patient who reacted only to severe painful stimuli, more on the right side than the left, although all limbs could be moved. The extremities were flaccid at rest. There was generalized hyporeflexia. Plantar response was diminished on the left. Abdominal reflexes were absent. The pupils were small but equal and reacted sluggishly to light. There was a tendency to conjugate deviation of the eyes to the right. The corneal reflexes were present. There was a questionable left central facial palsy. There were no signs of meningeal irritation. The impression was that of a cerebrovascular accident in the right hemisphere. The following morning she had a tonic convulsion and died two hours later, two days after the admission and approximately two weeks after the onset of the illness. Her terminal temperature was 104°F.

General necropsy findings. *Gross.* Petechial hemorrhages were present in the pericardium, myocardium, endocardium, liver, kidneys and adrenals. The spleen contained a small area of infarction. The vertebral bone showed normal trabeculation and bright red marrow.

Microscopic observations. Numerous capillary thrombi were found in all the viscera except the uterus. Thrombi were also found in arterioles in the heart, liver, kidneys, spleen, lymph nodes and bone marrow. None were observed in veins or lymphatics. Perivascular extravasations of red blood cells were present, especially in the heart. The spleen showed small areas of fibrosis—evidently healing infarcts—and one larger vessel showed an organizing thrombus. The lungs showed a large number of megakaryocytes, some within capillaries. The bone marrow was hyperplastic. It seemed normal in respect to ratio of the individual constituents.

Central nervous system. *Gross.* The only significant alterations were a few areas of reddish discoloration throughout the brain, particularly in the right anterior quadrigeminate body.

Microscopic observations. The cerebral cortex disclosed many thrombi in several stages of organization as noted in the previous case. There were numerous areas of ischemic necrosis displaying marked reduction in nerve and glia cells. There was a generalized increase of glial elements. No hemorrhages were noted. There were no thrombi in the subcortex but there were occasional slight perivascular infiltrations of small round cells and macrophages containing brownish pigment. Sections of the remaining portions of the brain and brain stem were essentially normal except for the presence of one thrombotic blood vessel in the midbrain.

Case 3. History. (Adm. #503426, P.M. #12468) The patient, a white female aged 33 years, entered the Mount Sinai Hospital on March 28, 1943. Two weeks earlier she began to complain of severe headaches, palpitations, buzzing in her ears and spots before her eyes. One week later she began to feel weak, was sleepy, disoriented, had difficulty in finding the correct words and walked unsteadily. A blood count revealed a severe anemia. Three days before admission the patient was transfused, after which she felt stronger and was more lucid. Her headaches continued, however, and she noted stiffness of her hands. At this time a low grade fever was noticed, but there were no chills, rash, joint pains or urinary abnormalities. On the morning of admission, the patient again became somnolent and disoriented and stiffness of the neck became apparent. Hematological studies just prior to hospital admission revealed hemoglobin, 34 per cent; red blood cells, 1,900,000;

reticulocytes, 22 per cent; platelets, 10,000; white blood cells, 7,800; myeloblasts, 6 per cent; segmented polys, 35 per cent; non-segmented polys, 31 per cent; lymphocytes, 21 per cent; monocytes, 6 per cent; eosinophiles, 1 per cent; normoblasts, 3 per 100 white blood cells. There was no history of bleeding tendency, allergy, previous acute infection, drug ingestion or contact with chemicals.

Examination. The patient was extremely pale and slightly jaundiced. Temperature was 101.6°F. Several purpuric spots were noted in the left buccal mucosa and on the dorsum of the right hand. There was no lymphadenopathy. Except for a tachycardia (110), the heart and lungs were normal. Abdominal examination was negative. Blood pressure was 120 systolic, 70 diastolic. No clubbing, cyanosis or edema could be detected.

Neurological examination. The patient was somnolent, disoriented and could be aroused only with difficulty. There was neck rigidity and a positive Kernig sign. The fundi showed slight blurring of the discs and many recent hemorrhages; all other cranial nerve functions were intact. The deep reflexes were active and equal. The superficial reflexes were sluggish. No pathological reflexes were elicited. Motor and sensory status were normal.

Laboratory data. Blood count done the day after admission (after a transfusion) revealed hemoglobin, 42 per cent; red blood cells, 1,950,000; white blood cells, 8,800. A few spherocytes were present. Red blood cell fragility was 0.64 per cent to 0.28 per cent saline; platelets, 10,000. Sedimentation time was 12 minutes. Coagulation time was 17 minutes and bleeding time was over 20 minutes. Tourniquet and pinch tests were strongly positive.

Sternal aspiration yielded marrow with a total nucleated count of 270,000; megakaryocytes, 176 per cubic mm. There was marked normoblastic hyperactivity, the normoblasts representing 63 per cent of the marrow differential. No abnormalities of the megakaryocytes were present.

On admission, blood chemical studies revealed cephalin flocculation, 1 plus; cholesterol, 220 mg. per cent; urea nitrogen, 10 mg. per cent; albumin, 3.9 Gm. per cent; globulin, 1.6 Gm. per cent with a total protein of 5.5 Gm. per cent; fibrinogen, 196 mg. per cent; ieterus index, 19; direct Van den Bergh, negative; indirect Van den Bergh, 2.15 mg. per cent; prothrombin index, 76 per cent.

The urine was cloudy with a specific gravity of 1.020. There were a faint trace of albumin, occasional white blood cells and several granular casts. Urobilinogen was increased (1:250), but no bile was present.

Lumbar puncture yielded crystal clear fluid under a pressure of 160 mm. There were 2 lymphocytes per cubic mm.; Pandy, 1 plus; total protein, 61 mg. per cent; Wassermann, negative.

Course. Immediately after admission the patient was transfused. Shortly after the transfusion, she became lucid and it was considered that the disorientation had resulted from cerebral anoxia rather than a cerebral hemorrhage. The purpura became much more prominent. Repeated blood transfusions were administered. On her third day in the hospital she became unresponsive to questions, but cried out whenever touched and began to bleed from the mouth, rectum and vagina. The next day a right facial paralysis developed. At this time, her temperature rose to 102.8°F. Because of the gravity of her condition and the poor response to transfusion alone, a splenectomy was regarded as urgent and this was performed on the fifth hospital day. The spleen was reddish-brown, moderately firm, weighed 165 Gm., and microscopically was found to be hyperemic, showing multiple thrombi in the arterioles of the pulp.

Following operation, the oral, rectal and vaginal bleeding continued and the general condition of the patient remained unchanged. The hemoglobin and red blood cells returned to the low levels found on admission. Platelets were 15,000; white blood cells, 41,000; myelocytes, 22 per cent; non-segmented polys, 50 per cent; segmented polys, 14 per cent; lymphocytes, 8 per cent; monocytes, 6 per cent; reticulocytes, 25 per cent; 10 normoblasts per 100 white blood cells. The ieterus index remained elevated, with normal values for blood urea nitrogen, chlorides and CO₂. Five days after operation a right hemiplegia de-

veloped. The right facial palsy persisted. She died the next day, 10 days after admission and 24 days after the onset of the illness.

Necropsy findings. Gross. The skin and mucous membranes were pale, slightly icteric and covered with multiple petechiae and purpura.

The abdominal cavity contained 300 cc. of bloody fluid. Multiple petechiae were visible in the visceral and parietal peritoneum. The *liver* extended 3 fingerbreadths below the right costal margin. Each pleural cavity contained 100 cc. of clear amber fluid.

The pericardial sac contained 100 cc. of clear yellow fluid. The pericardial surface of the heart was smooth and studded with many isolated and confluent hemorrhages. The myocardium on sectioning was pale red and showed many distinct pinhead-sized and small streaky hemorrhages and a number of indistinctly outlined pale yellow flecks.

Multiple subpleural petechiae were present. Both lungs were edematous, with firmer, somewhat collapsed bases. The cut surface was red, moist, and exuded a copious amount of frothy fluid; the bases of both lower lobes were airless and fleshy. The entire bronchial tree was filled with frothy fluid. There were numerous petechial hemorrhages, especially on the thoracic aspect of the diaphragm.

The *liver* showed subcapsular petechial hemorrhages. The sectioned surface was pale brownish-red with normal lobular architecture and a number of pinpoint-sized, dark red parenchymal hemorrhages. The pancreas, adrenals and thyroid were normal.

The *kidneys* appeared normal except for a number of pinpoint and streak-like hemorrhages within the medulla and cortex. There were large submucosal hemorrhages in both pelvis. The *bladder* showed only an occasional submucosal petechia. The *uterus* was distorted by multiple fibromyomata. The uterine cavity was filled with a large blood clot and the endometrium was hemorrhagic. The right ovary contained a large hemorrhagic corpus luteum.

The *stomach* and *small intestine* showed scattered submucosal petechiae while the *large intestine*, especially the distal portion, contained many hemorrhagic areas, some reaching 1 cm. in diameter.

The *vertebral bone* was pale, red and moist and presented normal trabeculation.

Microscopic observations. Pericardial hemorrhages and areas of acute pericarditis and myoearditis were present. Many of the terminal arterioles and capillaries were completely or partially occluded by recent thrombi or thrombi in various stages of organization. There was fatty infiltration, hemorrhage and fibrosis of the myocardium.

Marked edema was present in the lungs. Several arterioles contained thrombi.

There was a mild, diffuse, acute hepatitis. There was dense infiltration of portal fields by lymphocytes with a rare polymorphonuclear. Thrombi were present in many of the arterioles and capillaries in the portal fields. Both the central veins and portal veins were free of changes. There was evidence of extramedullary blood formation.

In the kidneys, the capillary loops of several glomeruli were occluded by thrombi. Some glomeruli showed focal obliteration of the capsular space; others showed partial fusion of the loops. There were foci of marked degenerative changes in the proximal convoluted tubules. Small vessels (arterioles and capillaries) in cortex and at the corticomedullary junction contained recent and organizing thrombi.

In the *pancreas* the arterioles and capillaries, including those within the islets, contained thrombi.

The *adrenals*, *colon*, and *lymph nodes* contained multiple arteriolar and capillary thrombi.

In the several sections of the *skin* studied, no thrombi were seen but there were extensive hemorrhages in the subcutaneous fat tissue.

Central nervous system. Gross. A cisternal puncture was performed before the removal of the brain and bloody cerebrospinal fluid obtained. There were scattered hemorrhages over the surface of the brain with a distinct area of recent extravasation, 1 mm. in thickness, over the right frontal lobe. There was extravasated blood at the base of the brain. On sectioning of the brain, no hemorrhage was found. There were some clots of blood ad-

herent to the dura over both hemispheres in the depth of the dorsal longitudinal fissure as well as over the dorsal portion of the dorsolateral surface of the hemispheres.

Microscopic observations. Only a single section of the cerebral cortex was available for histological study. This failed to reveal any thrombotic or other lesions and was also normal in other respects.

DISCUSSION

In one of the cases herein described in which only a small section of the cerebral cortex was available for microscopic examination, no thrombotic lesions were seen. In view of the apparently terminal focal neurological signs, it may be assumed that the characteristic lesions would have been found in the nervous system had more thorough histological examination been possible. The lesions in the nervous system in the two other cases are similar to those in previously reported cases. The lesions showed a striking predilection for the cerebral cortex and a surprising absence of outspoken parenchymatous changes. Indeed, there were areas of diffuse gliosis, softening and focal necrosis, with an occasional small hemorrhage, but none of these were of significant intensity. The case reported by Engel, Scheinker and Humphrey (10) is the exception, as here there were found small foci of softening associated with a dense glial reaction scattered through the cerebral cortex. The severity of these parenchymatous alterations may be explained by the fact that this patient had the longest period of survival, as he died approximately three months after the onset of his illness. It would appear that the initial thrombotic lesions are tolerated by the brain tissue, but in a more protracted course of illness with the further development of thrombotic lesions, a sufficiently large portion of the vascular supply to a given area is embarrassed to give rise to softening. Bernheim (7) states that the lack of significant parenchymatous necrosis in the majority of instances may be due to the fact that most of the involved blood vessels are not completely occluded and that the entire capillary bed in a given area does not seem to be involved. This lack of parenchymatous alterations in the nervous system as well as in the other viscera, may raise the further question of whether the thrombi are not agonal phenomena. However, in one of the cases reported here, where a splenectomy was performed a week before death, the spleen showed typical thrombotic lesions.

Of interest also is the observation that in this disease, in contrast to essential thrombocytopenic purpura without platelet thrombosis, there have been no instances of massive intracerebral hemorrhage. Subdural hematomata were found in the case reported by Singer, Bornstein and Wile (3) and in one of the cases reported here both subdural and subarachnoid hemorrhages were present.

The etiology of the thrombocytopenia, anemia and bleeding tendency is not known. There is apparently no deficiency in platelet formation since the number and form of the megakaryocytes in the bone marrow and platelet formation from megakaryocytes are normal. Bachr, Klemperer and Schiffrin (4) have suggested that the thrombocytopenia may be due to the withdrawal from the peripheral blood of the numerous platelets forming the thrombi. Singer, Bornstein and Wile (3) suggest that this mechanism may account for the thrombocytopenia but does not satisfactorily explain the bleeding tendency. There is good experi-

mental evidence to show that lack of platelets *per se* does not result in purpura; for bleeding to occur, the capillary endothelium must first be damaged, and this leads them to conclude that such a damaging "toxic" factor must be operative in this disease. They believe that the presence of such a toxic factor could also explain the hemolytic anemia.

The mechanism of the thrombotic phenomena is still not understood. Most observers agree that the endothelial proliferation is a secondary reaction to the presence of the thrombus rather than the cause of the thrombosis. This view is supported by the following observations in our material: 1) endothelial proliferation was found only in vessels containing thrombi, and 2) thrombi were present in vessels which did not exhibit endothelial proliferation. Several investigators however, have observed endothelial proliferation in blood vessels devoid of thrombi. In the opinion of Fitzgerald, Auerbach and Frame (2) the available evidence does not permit of a decision whether the endothelial damage is primary or secondary.

Baehr, Klemperer and Schifrin (4) suggested an allergic basis for this disease because of the similarity of the vascular lesions to those occurring in the Schwartzman phenomenon. In the Schwartzman phenomenon, however, severe hemorrhage and intense leukocytic infiltration of the walls of the blood vessels precede the appearance of platelet thrombi and, in addition, the lesions are located predominantly in the venules. These features are not present in generalized blood platelet thrombosis.

SUMMARY

1. Three cases of generalized blood platelet thrombosis are presented. This disease is an acute, fatal illness characterized by a low grade fever, thrombocytopenic purpura (including hemorrhagic manifestations), hemolytic anemia and generalized or focal neurological signs.

2. The pathological alterations consist of platelet thrombi in arterioles and capillaries; these are distributed throughout the body but are found most commonly in the central nervous system, myocardium, renal cortex, adrenals and pancreas.

3. In the central nervous system the thrombotic lesions are situated predominantly within the cerebral cortex and a conspicuous feature is the mildness, or complete absence, of parenchymatous alterations.

The authors wish to express their appreciation to Dr. Joseph H. Globus for his kind assistance in this study and in the preparation of this paper.

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DIENESTEROL, AN ORALLY ACTIVE SYNTHETIC ESTROGEN*

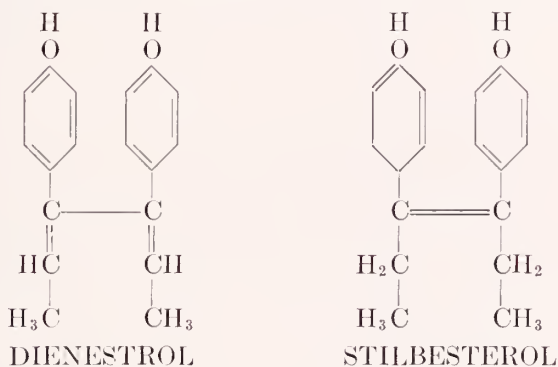
A CLINICAL EVALUATION

CHARLES S. POOLE, M.D., HILLIARD DUBROW, M.D., AND
ROBERT I. WALTER, M.D.

[From The Gynecological Out-Patient Clinic, The Mt. Sinai Hospital, N. Y. City]

The climacteric as an estrogen deficiency syndrome has been definitely accepted and established. Estrogen therapy in the menopause is substitution therapy and requires prolonged administration. The ideal estrogen should therefore meet certain requirements, i.e., high clinical effectiveness, low systemic toxicity, oral activity, low endometrial stimulation and low cost. Numerous estrogens meet these requirements in part. *Dienesterol*, a synthetic estrogen produced by Dodds and his coworkers (1) in 1938 would seem to fulfill many of these criteria.

The structural similarity of Dienesterol and Stilbesterol may be noted below:



In rodents it was shown that Dienesterol has a far greater estrogenic activity than any of the other available estrogens (2) (4). Barnes in 1942 (3) showed that Dienesterol was a potent estrogen when administered orally to humans. Since then several investigators (5) (6) (7) have studied the efficiency and dosage of this drug in the menopausal woman.

We wish to present our experience with Dienesterol in the treatment of the menopause in a series of 27 selected patients.

METHOD

The patients all exhibited classical menopausal symptoms such as flashes, nervousness, irritability, insomnia, restlessness, headaches, etc. The majority of them had previously received other estrogenic substances both orally and parenterally with varying degrees of relief. All medication was discontinued and following a rest period, the patients were given placebos, i.e., phenobarbital,

* The material for this study was supplied by E. R. Squibb & Sons, Inc.

or intramuscular saline injections, in an attempt to eliminate psychic factors. Only those patients who continued to have symptoms were selected for this study. Vaginal smear studies were done on all patients before and during therapy.

The initial dose of Dienesterol was 0.1 mg daily. This was gradually increased to the minimum amount necessary to obtain maximum clinical relief of symptoms. The cases were followed for periods of 3 to 8 months.

AGE

In this series of cases, 21 patients were in the natural menopause which varied in duration from 6 months to 15 years, the average being 5 years. The ages

TABLE I

TYPE OF MENOPAUSE	NO. OF CASES	AGE GROUPS	DURATION OF SYMPTOMS	AVERAGE DURATION OF SYMPTOMS
Natural	21	39 to 65	5 months to 15 years	5 years
Surgical	6	40 to 61	1 year to 17 years	7 years

TABLE II

NO. OF PATIENTS	APPROX. PER CENT OF PATIENTS	DOSAGE IN MG. DAILY
7	26	0.3
12	44	1.5
7	26	3.0
1	4	5.0

varied from 39 to 65 years. There were 6 surgical menopause cases varying in duration from 1 to 17 years, the average being 7 years. Their ages varied from 40 years to 61 years. (Table I).

DOSAGE

The average dosage necessary to obtain optimum relief of symptoms was 1.5 mg. daily given in divided doses. Seven patients, or approximately 26 per cent required 0.3 mg. daily, twelve patients, or approximately 44 per cent required 1.5 mg daily, seven patients or approximately 26 per cent required 3.0 mg, daily and one patient required 5.0 mg. daily to obtain maximum relief (Table II).

RESULTS

In this series of 27 cases, 24 patients obtained satisfactory relief of symptoms, 2 patients obtained fair relief and 1 patient was mildly benefitted (Table III). Similar good results have been reported by several investigators (5) (6) (7).

TOXIC EFFECTS

None of the patients in this series developed toxic symptoms such as nausea, vomiting, headache, etc., which occur not infrequently following the administration of stilbene derivatives. In only one instance did uterine bleeding occur. Slight spotting occurred for 5 days following the continuous administration of Dienesterol for 6 months. This ceased with the discontinuance of the drug.

The low incidence of uterine bleeding associated with the high therapeutic effectiveness of Dienesterol is worthy of emphasis. Unfortunately with many natural and synthetic estrogens, uterine bleeding is frequently induced with minimal effective dosage. This frightens the cancer conscious patient and places the conscientious physician in a quandary. Carcinoma of the female genital tract coincident with estrogen administration does occur and diagnostic curettage is the only certain method of differentiating between estrogen induced bleeding and carcinoma. In our experience there has been a sharp rise in the number of curettages performed in recent years because of estrogen induced bleeding. This procedure is necessary but economically wasteful.

TABLE III

NO. OF PATIENTS	APPROXIMATE PER CENT	DEGREE OF RELIEF
24	89	Marked to Complete
2	7	Moderate
1	4	Mild

Vaginal smear studies indicated that Dienesterol is capable of inducing estrogenic changes.

CONCLUSIONS

1. Twenty-seven selected menopausal patients were treated with Dienesterol.
2. Twenty-four patients obtained satisfactory relief, two patients obtained fair relief, and one was mildly benefited.
3. No toxic symptoms occurred in this series, and uterine spotting occurred in one case.
4. The low incidence of toxicity and uterine bleeding associated with the satisfactory therapeutic effectiveness make Dienesterol a valuable oral estrogen in the treatment of the female climacteric.

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MESOTHELIAL CYST OF THE DIAPHRAGM*

A CASE REPORT

ARTHUR AUFSES, M.D. AND ROBERT OSEASOHN, M.D.

Primary tumors of the diaphragm are not common. In a comprehensive survey of the literature, Scott and Morton (1) collected a total of 33 such growths up to 1946. Of these, 4 were not confirmed. Fourteen were considered malig-



FIG. 1

nant and 19 benign. To the latter group, the aforementioned authors added a case of primary cystic tumor of the diaphragm—making a total of only 3 such cases to be included in their review. In addition to the 3 cysts noted by Scott

* From the Surgical Service of Dr. Arthur S. W. Touroff, The Mount Sinai Hospital, New York.

and Morton, 2 others, one described by Pickhardt (2) in 1934, and the other described by Weber and Schwarz (3) in 1934, have been reported.

CASE REPORT

History. B. K., a woman, aged 42 years, was admitted to The Mount Sinai Hospital 4 months following the discovery of an intrathoracic tumor on routine x-ray examination of



FIG. 2

the chest. During the 3 months prior to admission, the patient's only significant symptom was pain in the chest posteriorly, which radiated anteriorly into the hypochondrium. This was described as a dull ache which was constant and unrelated to any activity or position. It had not increased in severity since onset. Six years prior to admission, an adenoma had been removed from the thyroid gland.

Examination. The positive physical findings included: Blood pressure, 130 systolic and 90 diastolic; a well-healed thyroidectomy scar, a barely palpable liver edge and bilateral internal saphenous vein varicosities. Roentgen study in the P-A position, revealed a rounded mass, 1 to 1½ inches in diameter, in the right cardiophrenic angle (fig. 1). In the

lateral position, the lesion was located anteriorly to the midpoint of the diaphragm, with which it appeared to be intimately associated (fig. 2). No calcification was noted. The roentgen appearance suggested the diagnosis of benign tumor of the diaphragm. Bronchoscopy was non-contributory. Radioactive iodine studies were carried out by the Radio-physics Department of the Hospital in conjunction with the Tumor Clinic, where this patient was first seen. No pickup of the radioactive substance was noted, thus ruling out the diagnosis of a functioning metastatic tumor arising from the thyroid gland. Complete blood count, erythrocyte sedimentation rate, urinalysis and blood chemistry were all within normal limits.

Course. The diagnostic possibilities in this case included carcinoma of the lung and several pathologic states of the diaphragm, among which tumor, hernia and other congenital anomalies were considered. Because of the excellent general status of the patient, the absence of any lymphadenopathy, the negative findings on bronchoscopy and the roentgen appearance, exploratory thoracotomy was performed.

At operation, a clear-water cyst was found arising from the diaphragm close to the right cardiophrenic angle with the fibers of the right phrenic nerve coursing over its surface. The surgeon was able to remove the cyst completely from its attachments to the diaphragm. The patient made an uneventful recovery. Pathologic examination revealed the wall of the cyst to be thin and fibrous with a flattened surface lining. Some lymphatic tissue was found in the wall. Pathologic findings were compatible with mesothelial cyst.

Comment. This is the sixth case of primary cystic tumor arising from the diaphragm to be reported. The type of pain noted by our patient is one of the most common symptoms of primary tumor of the diaphragm.

Additional diagnostic aids when dealing with intrathoracic tumors intimately associated with the diaphragm are pneumothorax, pneumoperitoneum and thoracoscopy. Calcium deposition in the cyst wall should suggest the possibility of echinococcal infestation, and under such circumstances further studies should be made.

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OCCLUSION OF THE ANTERIOR SPINAL ARTERY

A CASE REPORT¹

SANFORD PARISER, M.D., AND LOUIS LASAGNA, M.D.

Vascular accidents occur in the spinal cord with relative infrequency in comparison to their occurrence in the cerebrum. Occlusion of the anterior spinal artery is a rare neurological entity. The clinical picture is striking and permits an accurate clinico-pathologic correlation. The following case is presented as a classical example of this syndrome.

CASE REPORT

History (Adm. #569369). The patient, A. R., a white Polish male laborer aged 55 years, was said to be well until 36 hours prior to his admission to the Mount Sinai Hospital on August 26, 1947, when he suddenly developed numbness and tingling of the hands, gradually spreading to involve the forearms. Shortly thereafter he noted progressive weakness of the hands and arms and, later in the day, weakness of the legs. He finished work and walked home in the evening with some difficulty. Upon arriving home he complained of weakness in all extremities, chiefly the upper, and loss of sensation over the extremities and abdomen. He was unable to void or move his bowels. Because of suprapubic distress, a hot water bag was applied to the abdomen. Vesicles appeared, yet the patient experienced no pain. On the morning of admission, the patient fell to the floor while attempting to get out of bed.

Examination. The patient was a well developed, well nourished white male who lay in bed with the arms flexed and the fingers partially flexed. The chest was emphysematous and no costal excursions could be observed with respiration. The abdomen exhibited second degree burns. The bladder was enlarged up to the umbilicus. The rectal sphincter was patulous. The blood pressure was 120 systolic and 80 diastolic.

Neurological findings. There was ptosis of both upper eyelids and a bilateral Horner's syndrome, with enophthalmos, miosis, narrowed palpebral fissures, and anhidrosis of the face. Instillation of 4 per cent cocaine solution failed to produce dilatation of the pupils. The patient was unable to stand. There was marked weakness in all four extremities. Weakness was greatest in the triceps, wrist flexors, and intrinsic and extrinsic muscles of the fingers. Weakness in the lower extremities was greater on the right than on the left. The deep tendon reflexes were equal and active throughout except for the triceps jerks which were absent bilaterally. The abdominal reflexes were markedly diminished. The cremasteric reflexes were absent. There was bilateral absence of plantar flexion. There was marked reduction of pain and temperature sensation bilaterally below C-7 and C-8, with impairment greater on the left than on the right. The senses of position and vibration were intact. Sweating was absent below the costal margins bilaterally.

Laboratory data. White blood cells, 11,500, with a normal differential; hemoglobin, 105 per cent. Blood Wassermann and Kahn tests, negative. Urine, normal; fasting blood sugar and blood urea nitrogen, normal. Blood cholesterol, 320 mg. per cent. X-ray examination of the skull and spine was negative. An electrocardiogram was normal. A lumbar puncture yielded normal cerebrospinal fluid with normal dynamics. Fluoroscopy of the chest showed good motion of the diaphragms.

Course. Shortly after admission, the patient was catheterized and approximately 1000

¹ From the Neurological Service of Dr. I. S. Wechsler, The Mount Sinai Hospital, New York.

cc. of urine were removed. Following this he voided spontaneously and required no further catheterizations. On the second hospital day the patient was able to stand with assistance. At this time it was noted that the abdominal reflexes had entirely disappeared. A sweating test performed at this time, using starch-iodine powder in a heater cabinet, showed bilateral anhidrosis of the face as well as of the C-4 dermatome. Skin temperature tests showed no gross deviations and chronaxie studies were within normal limits.

By the fourth hospital day there had been a marked improvement in the patient's condition. He now was able to stand and walk unassisted. The triceps jerks had returned as had some power in the triceps muscles. Coincident with this improvement, there was some return of pain and temperature sensation bilaterally, greater on the right than on the left; and sensation was entirely normal between T-2 and T-6. However, there was some impairment bilaterally below the level of T-6 and also in the distribution of C-8 and T-1.

The clinical course thereafter was one of gradual improvement in sensation and muscle strength, particularly in the lower extremities. On the 8th hospital day a Babinski sign was noted on the right side for the first time. Cystometric examinations performed at this time were reported as normal. By the 13th hospital day no abnormalities of sweating could be detected.

At the time of discharge, Sept. 18, 1947, 24 days following admission, the patient was able to walk with a slightly dragging gait. The hands were held partially flexed. The weakness of the intrinsic and extrinsic muscles of the hands persisted, though at this time the patient was able to hold a glass in both hands unassisted. All deep reflexes were hyperactive. Babinski signs were not elicited. Sensation over the right side of the body was normal. Pain and temperature sensation was diminished over the left side up to the costal margin and over the fifth finger of the left hand. The bilateral Horner's syndrome was still present. Treatment had consisted of prophylactic chemotherapy early in the course, plus supplemental vitamins, liver, and physiotherapy. The patient was returned to the care of his private physician.

Two months following the onset of his illness, the patient was seen in Follow-Up Clinic (October 23, 1947), when his main complaint was weakness of the hands. His general condition had slowly improved. The gait still showed slight dragging. Motor power was good except for flexion and extension of the fingers and wrists which were quite weak. The patient was unable to close fully the right hand. The deep tendon reflexes were equal and active throughout. There was a moderate loss of pain sensation in the left lower extremity; proprioceptive modalities, however, were intact. There was a questionable Babinski sign on the right.

COMMENT

The recognition of this syndrome depends on the knowledge of the anatomic distribution of the anterior spinal artery. This vessel is formed by the union of the more rostral of the two pairs of arterial branches arising from the vertebral arteries. Below the fourth or fifth cervical segment, the artery is formed by the union of the lateral spinal arteries, and receives numerous anastomosing branches from the intercostal and lumbar arteries. All these branches unite in the midline to form the anterior spinal artery, which supplies the ventral and lateral horns, the central grey, Clarke's column, and the ventral and lateral white funiculi, including the lateral pyramidal tract—thus, the entire cord except for the dorsal horns and dorsal white columns is supplied by this vessel. Thrombosis of the anterior spinal artery, therefore, cuts off the blood supply to the anterior grey matter and the spinothalamic, pyramidal, and other tracts situated in the anterolateral columns of white matter (see diagram).

The clinical manifestations in occlusion of the anterior spinal artery vary with the site of the occlusion, but they are marked by the sudden loss of power in the extremities, as well as by the dissociated anesthesia of the syringomyelic type below the level of the lesion, the latter characterized by loss or diminution of the sensations of pain and temperature with preservation of posterior column modalities. There may be sphincteric disturbances causing distressing difficulties in urination and defecation. Occlusion of the vessel at the level of the cervical enlargement produces, in addition to the foregoing signs and symptoms, a spastic

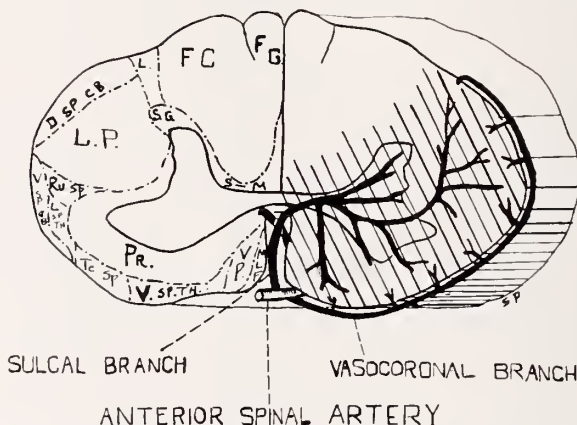


FIG. 1. Cross-section of spinal cord at lower cervical level. On the left are shown the tracts; on the right, the sulcal and vasocoronary branches of the anterior spinal artery and their distribution. It will be noted that the sulcal branch is unilateral. Another sulcal branch may be seen supplying the left side of the cord. The hatched area, affected by occlusion of the anterior spinal artery, is shown on the right for purposes of illustration but should be bilateral.

Legend: F.C., Fasciculus cuneatus; F.G., Fasciculus gracilis; L. Lissauer's tract; S.G., Substantia gelatinosa; S.M., Septomarginal tract; D.Sp.cb., Dorsal spinocerebellar tract; V.Sp.cb., Ventral spinocerebellar tract; L.P., Lateral corticospinal tract; Ru.sp., Rubrospinal tract; L.Sp.th., Lateral spinothalamic tract; Tc.sp., Tectospinal tract; V.Sp.th., Ventral spinothalamic tract; V.P., Ventral corticospinal tract; M.L.F., Medial longitudinal fasciculus.

paraplegia in the lower limbs and an atrophic flaccid wasting of the muscles of the upper extremities.

Occlusion at the cervical level is the commonest location. Involvement of the vessel supplying thoracic segments will produce a similar picture below the lesion with sparing of the upper extremities. A third variety occurs when the pathological changes are confined to the lumbar region and is typified by an atrophic paraplegia.

While the case lacks pathological confirmation, the clinical diagnosis of anterior spinal artery thrombosis seems fully justified. The cause considered to be most probable was arteriosclerosis, since lues, embolism, blood dyscrasia, tumor, abscess, osseous disease and trauma seem to have been ruled out. Hematomyelia, a condition most frequently confused with this syndrome, seemed unlikely inasmuch as the fibers of the posterior columns were not implicated and there was no history of trauma.

Two unusual features of this case bear mention. The first was the presence of a bilateral Horner's syndrome, indicative of the implication of the visceral column of cells or the ciliospinal bundle at the level of C-8 and T-1. In a review of seven cases of occlusion of the anterior spinal artery, Zeitlin and Lichtenstein (4) make no mention of a concomitant Horner's syndrome.

The second feature was the presence of a partial Brown-Séquard syndrome, as it will be noted that there was greater loss of motor power on the right side where a Babinski sign appeared, and that impairment of pain and temperature was greatest on the left side. An explanation for the asymmetry of the signs suggestive of a Brown-Séquard picture in this case may be sought in the work of Herren and Alexander (2). These authors studied the blood supply of the human spinal cord and found that the branches of the anterior spinal artery, the anterior sulcal arteries, pass upward through the anterior sulcus and furnish blood to only one side of the cord, either the right or the left. It may well be that in our case, occlusion was not complete (as evidenced by the degree of recovery experienced by the patient), but that an anterior sulcal branch supplying the right side of the cord was occluded to a greater degree than other branches with a concomitant greater motor loss on the right and sensory loss on the left.

Treatment in instances of anterior spinal artery occlusion is usually directed at the prevention of complications and at attempts to maintain muscular integrity. In cases in which the age and condition of the patient, the extent of the lesion and its cause do not preclude response to remedial measures, a considerable degree of functional restitution may occur, as in our case.

SUMMARY

A case clinically diagnosed as one of anterior spinal artery occlusion is described and the salient features in the clinico-anatomical correlation are discussed.

We wish to thank Dr. Morris B. Bender for his help and encouragement in the writing of this paper.

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ALLERGIC EUSTACHEITIS¹

SHEPPARD SIEGAL, M.D.

The occurrence of an allergic reaction taking place in the region of the Eustachian tube orifices, and possibly in the tubes themselves, as the dominant clinical manifestation of pollen sensitivity is illustrated by the case herein reported. A survey of the literature has not revealed another published instance of this kind.

Sensations of fullness or of itching in the ears may occur as an incidental discomfort in the course of hay fever or vasomotor rhinitis. Menière's syndrome due to food allergy has been reported, and Fuchs and Almour² described a very unusual case of recurrent nerve deafness caused by an allergic reaction to several foods and inhalants. In their case the allergic response was thought to take place in the internal ear; the Eustachian orifices were found normal.

CASE REPORT

History: M. S., a male, aged twenty-nine, developed in May of 1945 following a "cold" a whistling sound and very severe pain in the ears. When the pain was intense it tended to radiate into the suboccipital area, constituting what the patient described as a very severe headache. The symptoms continued with unabating severity until October of that year, when they subsided considerably, but nevertheless persisted throughout the winter and into the spring. Again there was a sharp flare-up of his ear symptoms in May of 1946, lasting throughout the summer and attaining a crescendo of discomfort in September of that year.

His past history was essentially negative except for an occasional swelling of the upper lip, presumably due to angioedema. No member of his immediate family has had any allergic manifestation. A maternal cousin had had hay fever.

Apart from an initial transitory rhinitis, the patient denied having any further nasal symptoms indicative of hay fever. He had no sneezing, rhinorrhea, nasal obstruction or post-nasal discharge; he had no itching of the eyes, ears, nose or throat; and none of these symptoms has appeared at any time during the three years that he has been under observation.

On close questioning he has denied any indication of impaired hearing or vertigo. The sole additional symptom which the patient has associated with his primary complaints of ear pain and tinnitus, has been occasional severe pain in the left eye. This pain tends to occur especially when his ear symptoms are severe. The eye appears normal externally at such times, and ophthalmic examination is negative except for the presence of congenital nystagmus.

During the months following the onset of his present illness, the patient had numerous intranasal treatments and was seen by several ear, nose and throat specialists. He was also given a course of histamine desensitization. He derived no benefit from these forms of therapy.

¹ From the Allergy Section of the Medical Services, Mount Sinai Hospital, New York.

² Fuchs, A. M. and Almour, R.: Allergic Deafness, New York State Journal of Medicine, 47: 1397-1398, June 15, 1947.

Re-examination of ear, nose and throat showed: otoscopic examination was negative. Audiometric study revealed slight bilateral receptive impairment, air conduction being better than bone conduction. Cold caloric response was normal. X-ray films of the internal auditory meati and skull were negative. Slight edema of the turbinates was present. Irrigation of the left sphenoid yielded muco-purulent secretion on one occasion, but thereafter the returns from both sphenoid and maxillary sinuses were clear. On nasopharyngoscopy a retained abscess in a cystic scarred adenoid mass was incised and drained on the right side. It was noted that the Eustachian orifices were unusually prominent and edematous.

The local procedure did not afford any relief and because of the striking localized edema, an allergic investigation was suggested.

In February of 1947, when this patient was first seen by me, his ear complaints had continued, although in a mild degree, after the previous fall exacerbation. Because of the clear cut seasonal recurrence of his symptoms, a pollen factor was suspected. This suspicion was confirmed by the finding of markedly positive intradermal reactions to grass and ragweed pollen extracts, and also to house dust. Slight reactions were present to feathers, horse dander, pyrethrum, orris, cottonseed, kapok, tobacco and mixed tree pollen. The following food extracts gave moderate reactions on testing: lamb, barley, oats, rice, rye, wheat, garlic, lima bean, onion, green pea and banana. Nasal smears showed epithelial cells but no eosinophiles.

Allergen-proof casings were advised, house dust precautions and avoidance of other positive inhalant factors were urged. The patient was given a trial of anti-histamine drugs; he did not respond. In March specific desensitization was begun with extracts of ragweed, grass and house dust.

During the grass hay fever season of 1947, he had very slight ear symptoms, much less acute than in previous years, but in the fall season he again experienced an acute flare-up in September. The maximum ragweed dose at this time was 9,000 protein nitrogen units. With perennial treatment continuing into 1948 and a consequent increase in the top pollen dose to 18,000 units, this patient had an extremely comfortable spring and fall season without any return of acute ear or head pain and tinnitus. He also observed that his perennial symptoms had almost completely disappeared. For a few days in mid-October he had a brief recurrence of pain for which there was no obvious causative factor. A previous trial diet excluding the skin test positive foods and their subsequent reinclusion, had indicated that food allergy played no role in his condition. Retesting at this time with mold extracts failed to discover any mold allergy as a possible additional excitant. However, this patient is well satisfied with the results of allergic treatment for a condition which he insists is "hay fever of the ears".

SUMMARY

A man, aged twenty-nine years, complained of intense pain referred to both ears, accompanied by sub-occipital headache and whistling tinnitus of two years duration. Increase of these symptoms to an acute stage occurred each year in the spring and fall. There was striking absence of the usual nasal and ocular

symptoms of hay fever. Nasopharyngoscopic examination showed marked edema of the orifices of the Eustachian tubes. Skin tests yielded marked positive reactions to ragweed and grass pollens and to house dust, as well as to other inhalant and food allergens. Specific desensitization with the pollens and house dust and general allergic management afforded marked relief not achieved by previous local treatments or with the anti-histamine drugs.

ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Experimental Impairment of the Gastric Mucous Barrier in Dogs. F. HOLLANDER, B. P. SONNENBLICK AND H. A. SOBER. J. Nat. Cancer Inst., 7: 361, April, 1947.

The existence of a mucous barrier, consisting of a layer of mucus and one of readily replaceable columnar epithelium, may serve to explain the failure of malignant tumors to develop in the stomach following oral administration or direct application of carcinogens. Hence, experiments were carried out in an effort to damage the gastric mucous barrier in Heidenhain pouch dogs and to investigate its subsequent recovery. Repeated application of eugenol emulsion progressively denuded the mucosa of its mucus secretion, the protective layer of columnar cells, many neck chief cells, and even some parietal cells. There was also evidence of considerable inflammatory reaction of the tissue, which increased with successive applications of the irritant. The tissue recovered only a part of its mucus-secreting function after 36 hours. Three months later, recovery was still only partially complete, and the tissue showed marked evidence of fragility. With the knowledge thus obtained, it may be determined whether experimental carcinogenesis is possible after such impairment.

A Rare Anomaly of the Cystic Duct. H. E. LEITER. Surg. Clin. North America, 27: 389, April, 1947.

An unusual anomaly was described wherein the cystic duct emptied into the right hepatic bile duct. This complicated the surgical procedure in that the resection of a common bile duct carcinoma necessitated a separate right and left hepatic duodenostomy.

Bleeding as a Late Sequel of Subtotal Gastrectomy of the Billroth II Type for Duodenal Ulcer. S. MAGE. Surg. Clin. North America, 27: 241, April, 1947.

In a series of 456 patients, who had been followed for a year or longer after undergoing subtotal gastrectomy of the Billroth II type for duodenal ulcer, 23 are known to have had gross hemorrhages; i.e. either melena or hematemesis. The hemorrhages occurred at intervals varying from a few months to 12 years after operation. 12 of the 23 patients had also bled prior to operation. Bleeding, manifested by melena or hematemesis, with or without pain, occurs sufficiently often after subtotal gastrectomy of the Billroth II type for duodenal ulcer to be recognized as a significant late sequela of that operation. When the bleeding is painless, it is usually due to superficial ulcerations or erosions in the jejunum or at the gastro-enteric stoma, and as a rule responds to conservative treatment. If the bleeding is associated with pain, it is invariably due to an active penetrating ulcer. This type of case does not ordinarily respond to medical measures, and further radical surgery, as a rule, is contraindicated because of its great hazard and doubtful therapeutic outcome. The operation of vagotomy, on theoretical grounds, offers promise of particular benefit, but its ultimate evaluation requires further experience with its use.

Early Postoperative Motor Response of the Small Intestine to Jejunal Feedings. S. ROSENAK AND F. HOLLANDER. Surg. Clin. North America, 27: 345, April, 1947.

The intestinal motor response to the predigested synthetic aliment previously reported

was studied at various time intervals after abdominal surgery, which varied from simple jejunostomy to subtotal gastric resection. The time between surgery and the first jejunal feeding was 24-40 hours. The meal, with barium added, passed into the ileum in all cases within 3 hours and reached the cecum in 5-20 hours. In 3 cases examined 3-5 weeks later, intestinal propulsion of the aliment was more rapid. Early post-operative cases showed no ileal distention nor regurgitation of the meal into the duodenum. It is concluded that jejunal feeding is a safe procedure 24 hours after abdominal surgery provided certain precautions are observed in regard to its administration.

Excretion of Benzoyl Glucuronate as a Test of Liver Function. I. SNAPPER AND A. SALTZMAN. Am. J. Med., 2: 334, April, 1947.

A simple liver function test is described which is based on the presence of excessive excretion of benzoyl glucuronate in the urine after ingestion of 5 Gm. of benzoic acid. The test is non-toxic and can be performed quickly. In selected cases, when used in conjunction with the current liver tests, it has important diagnostic application. In all cases of hepatitis and portal cirrhosis, in some patients with thyrotoxicosis, and in hepatic metastasis the test was positive. Application in 2 cases of early-type post-arsphenamine jaundice is described. In both cases hepatocellular damage was indicated by positive tests. In one the diagnosis of arsphenamine hepatitis was made in the presence of gallstones.

Quantitative Aspects of Benzoyl Glucuronate Formation in Normal Individuals and in Patients with Liver Disorders. I. SNAPPER AND A. SALTZMAN. Am. J. Med., 2: 327, April, 1947.

Patients with impairment of liver function excrete considerable quantities of benzoyl glucuronate after administration of 5 Gm. of benzoic acid. The qualitative glucuronate reactions in the urine are negative in normal persons and the amount of total benzoic acid is equal to the quantity of benzoic acid excreted in the form of hippuric acid. Under the same conditions the qualitative glucuronate reactions in the urine are positive in patients with impaired liver function, and the amount of total benzoic acid exceeds the quantity of benzoic acid excreted in the form of hippuric acid by 5.8 to 49.8 per cent.

The Roentgen Differentiation of Benign and Malignant Ulcers. M. L. SUSSMAN AND J. J. LIP-SAY. Surg. Clin. North America, New York No., p. 273, April, 1947.

The authors offer a helpful study in an attempt to further the diagnostic criteria in differentiating benign and malignant ulcer of the stomach. In presenting the basic pattern of benign gastric ulcer, emphasis is placed on the roentgenologic demonstration of a smooth rounded projection outside of the gastric contour with no loss of flexibility of the gastric wall. There is no significant alteration of the width or distinctness of the mucosal folds and they may radiate toward the niche. The malignant ulcer represents in most cases an eroded neoplasm in which the niche is a part of the neoplastic process and is in turn characterized by loss of flexibility of the involved gastric segment which is indented or depressed into the gastric contour. The adjacent mucosa is likely to be altered. Benign ulcer complicated by such factors as healing, deposition of food, mucus or blood clot, inflammatory edema, etc. may well lead to confusion and error. Location of the niche, size and depth of crater, spastic phenomena and other lesions associated with the ulcer constitute indirect signs in further differentiation. Diminution in the size of the niche and its eventual disappearance are, of course, considered reliable signs of benignancy. Lack of regression on active therapy must be regarded as suggestive of neoplasm. The statement is made and repeated to the effect that roentgen examination often does not provide an unequivocal differentiation between benign and malignant ulcer. Clinical and laboratory correlation is essential. It is carefully stressed, however, that the roentgen examination is most informative and should be universally applied.

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SYSTEMIC PATHOLOGY CONSEQUENT TO TRAUMATIC SHOCK*

TRACY B. MALLORY, M.D.

*Professor of Pathology and Acting Chairman of the Department of Pathology,
Harvard Medical School, Boston, Massachusetts
Chief of Pathology Laboratory, Massachusetts General Hospital, Boston*

To demonstrate a relationship between a parenchymal degenerative change or pattern of changes and the clinical state of shock, several conditions must be satisfied. The lesions must first be sufficiently distinctive, so that there can be no possibility of confusion with postmortem degeneration or the artifacts of poor fixation and faulty histologic technique. Second, they must be clearly distinguishable from the group of agonal changes seen in the tissues of any individual whose death has not been instantaneous or at least relatively rapid. Specificity of individual lesions cannot reasonably be expected, but the changes should be demonstrable in a high proportion of shock cases, absent in cases of sudden death, and relatively infrequent in cardiac, metabolic, or cerebral deaths in which shock-like states are comparatively uncommon. There should be a demonstrable time-relationship between the onset of shock and the appearance of the lesions, and conversely between recovery from shock and their disappearance. So far as I have been able to ascertain, no pattern of lesions which fulfills these conditions in man has been described.

The anatomic changes associated with shock may be usefully divided into 1) those which occur concomitantly with the state of shock and therefore are of interest in relation to its pathogenesis and 2) those which follow shock and therefore may be considered as its consequences. In studies of the pathology of human shock (1, 2), attention has heretofore been concentrated on the former; in the present work, it is particularly devoted to the latter.

Our own search for anatomic lesions characteristic of shock was at first dominated by the concept of concomitant lesions. The postmortem material from several hundred battle casualties was vainly examined for any lesion or combination of lesions which would fulfill the imposed conditions. The organs of patients dying after 4, 8 or 12 hours of prolonged shock showed little evidence of histologic change and none which could not readily be duplicated in a series of non-shock cases.

When, however, attention was turned to patients who survived 18 or more hours after a shock-producing injury and when frozen sections stained for fat with Sudan IV were substituted for paraffin sections, a fairly constant pattern was disclosed. Evidence was obtained that approximately 18 hours after a shock-producing injury fat vacuolation appears in the parenchymal cells of the

*Presented as one of the series of lectures on Recent Advances in Pathology and Bacteriology, at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, March 2, 1949. Reproduced here in abstract form.

heart, liver and kidneys. These changes increase in frequency and severity up to 96 hours after injury, then progressively decline with longer periods of convalescence from the episode of shock unless complicating factors, such as fat embolism or severe infection, prevent resolution of the process.

In the adrenal gland a group of changes was readily demonstrable: swelling of the cortex, pseudotubular degeneration and depletion of lipid, particularly of doubly refractile lipid. Since these changes do not differ qualitatively and are less marked quantitatively than those seen in cases with infection and in other types of control material, their significance is questionable. Only one factor, the depletion of doubly refractile lipid, showed a tendency to reversibility with increasing time intervals following resuscitation from shock.

In addition to this group of reversible parenchymal lesions, which were present in a high proportion of all shock cases investigated, one usually irreversible lesion, the so-called lower nephron or hemoglobinuric nephrosis, appeared in the kidneys of a limited number of the patients. The morphologic characteristics of this lesion have been described so frequently (3, 4, 5) that repetition would be profitless but the evidence for considering it a consequence of shock is worthy of examination.

MATERIAL

The nucleus of material for this study was provided by the clinical records and autopsy material of 60 fatal battle casualties studied by a Military Board¹ organized as a research group and attached to various hospitals in the 5th Army Area during the last nine months of the Italian campaign. As work progressed, the importance of sepsis as a complicating factor became apparent and it was necessary to supplement the original material with additional cases from the files of the 15th General Laboratory in which major sepsis could be excluded and which covered time ranges not included in the Board cases. Control material was drawn from the 15th Laboratory and from the Army Institute of Pathology. The majority of necropsies were performed under field conditions by an officer of a Field or Evacuation Hospital whose experience in pathology was often limited. Examinations and records were inevitably incomplete. Blocks of representative tissue were fixed in formalin, occasionally in Zenker's solution, and transmitted to the 15th Laboratory where the sections were reviewed by the author.

OBSERVATIONS

Heart. Material was available for fat stains from 55 shock cases. Abnormal fat vacuolation was found in 17. This consisted of very minute droplets, seldom more than 2 microns in diameter, arranged in parallel rows between the myofibrils. When present in a cell, the vacuolation was apparent throughout the cell's length and breadth, rarely segmentally or focally. It was entirely independent of the amount of lipochrome visible at the nuclear poles. The affected cell often seemed slightly swollen in the frozen section but this change could not be recognized with certainty in the paraffin sections. Sometimes single cells, more often groups of from 10 to 50 adjacent fibers were affected. Vacuolation was never diffuse throughout the myocardium. In appearance it was strongly reminiscent of, though usually less severe than, the patchy fat vacuolation seen in severe anemia. However, no gross changes suggestive of "tigerling" were ever noted.

¹Board for Study of Problems of the Seriously Wounded, NATOUSA: Lieutenant Colonels Henry K. Beecher, Tracy B. Mallory, Fiorindo Simeone and Eugene Sullivan Major Charles Burnett, and Captains Seymour Shapiro and Louis Smith.

The severity of the change, estimated by the number and size of vacuoles per cell and the proportion of cells involved, was roughly quantitated on a zero to 3-plus scale. The degree of involvement is compared with the survival period in Table 1.

It is evident that fat vacuolation of cardiac muscle cells was not observed in previously healthy young men who developed shock following trauma but failed to survive at least 18 hours. In patients manifesting shock who lived from 18 to 96 hours, fat vacuolation of the myocardium was found in 75 per cent. With longer periods of survival, the incidence dropped sharply to 17 per cent and there were no cases of grade 3 severity.

TABLE 1
*Myocardial Fat Vacuolation in 55 Shock Cases**

GRADE OF FAT VACUOLATION	SURVIVAL PERIOD		
	Less than 18 hours	18 to 96 hours	More than 4 days
0	10	4	24
1+	0	4	2
2+	0	2	3
3+	0	6	0
Percentage positive	0	75%	17%

* In this and subsequent tables, figures in columns indicate number of cases unless otherwise specified.

TABLE 2
*Degree of Shock and Fat Vacuolation of Myocardium in 14 Patients who Survived from 18 to 96 Hours**

DEGREE OF SHOCK	GRADE OF FAT VACUOLATION			
	0	1	2	3
Slight	0	0	1	0
Moderate	1	2	1	1
Severe	2	1	0	5

* Figures indicate number of cases in each category.

In Table 2, the 14 patients who died within the 18 to 96 hour period and who had been examined during life by a clinical member of the Board are tabulated according to the degree of shock and the severity of fat vacuolation. The number of cases is small but the increasing intensity of fat vacuolation as shock becomes more severe is apparent.

Control Cases. In Table 3, a group of 51 control cases is listed. These include a number of instances of sudden death and a miscellaneous group of medical conditions. Since fat vacuolation can be produced in experimental animals by short periods of starvation (6), it seemed appropriate to study some cases from prison camps of death by starvation and, as fatty change in the myocardium has long been recognized as a sequel of severe

anemia, a series of cases of aplastic anemia was included. Analysis of the material from the point of view of the presence or absence of peritonitis, an important factor in relation to liver and adrenal lesions, yielded no evidence that this type of infection was important in the production of the myocardial changes.

Summary. Fat vacuolation of cardiac muscle fibers is a pathologic process not seen in previously healthy persons who die suddenly or who die following a shock-producing injury in a period of less than 18 hours. It is found in 75 per cent of individuals who have survived a similar injury for periods of 18 to 96 hours but becomes unusual in those living more than 4 days after injury. In a small sample group, the degree of fatty change appeared to parallel the severity of shock. Though the lesion is found inconstantly in a variety of medical conditions, particularly those associated with severe grades of anoxemia, the frequency is considerably below that observed following shock.

Liver. Fat vacuolation of the liver appears in such a variety of circumstances and may be present in so many apparently normal individuals that one is tempted to regard it as not significant unless the amount is very great. The usual form observed consisted of vacuoles of considerable size, ranging from 5 to 20 microns in diameter. Fat vacuola-

TABLE 3
Fat Vacuolation of Myocardium in 51 Control Cases

NUMBER OF CASES	TYPE OF CASE	GRADE OF FAT VACUOLATION				PERCENTAGE POSITIVE
		0	1	2	3	
15	Sudden deaths	15	0	0	0	0
12	Starvation	12	0	0	0	0
9	Aplastic anemia	6	0	2	1	33
15	"Medical" deaths	11	2	1	1	27

tion of this type is rarely seen in shock, and when found probably existed before the shock-producing injury. Extensive fat vacuolation was nevertheless readily demonstrable in shock if sufficient time had elapsed for its development. This form of fat vacuolation consisted almost entirely of very fine droplets in the range of 2 to 4 microns in diameter. They showed little tendency to fuse and as many as 15 to 20 may be present in a single cell. The affected cells in the initial stages were always centrally located in the lobule; with increasing severity, the involvement spread to the periphery. There was little evidence of swelling of the cells and the organ as a whole was not enlarged, yellow or greasy. For this reason, it seems improbable that the amount of fat in the liver can have been greatly increased.

The occurrence of small-droplet fat in relation to survival period in 53 shock cases is shown in Table 4. All cases complicated by major infection have been excluded since this factor likewise influences the appearance of small droplet fat.

It is apparent that fat vacuolation of more than minimal degree was seldom seen in shock patients who failed to survive at least 18 hours. Of those who survived from 18 to 96 hours, 87 per cent showed the presence of fat, 59 per cent in moderate or severe degree. With survival beyond 96 hours, a tendency to return to normal is seen, the total dropping to 47 per cent and that for the severer grades to 29 per cent.

Control Cases. Since fat vacuolation of the liver is such a common phenomenon and can be produced by so many etiologic factors, numerous control cases seemed necessary. Seventeen cases of sudden death were selected at random from the laboratory files. To

these were added 15 cases of "medical" deaths without obvious shock-like states (cardiac, cerebral and nephritic), 20 cases of aplastic anemia and 38 deaths associated with starvation—a total of 90 control cases. The incidence of centrolobular fat vacuolation is shown in Table 5.

The occurrence of moderate to severe fat vacuolation in 24 per cent of the sudden death group is worthy of comment. This group was compiled largely from accident and homicide cases in base section troops and the proportion of limited service and older men is higher than in combat organizations. Two of the men had been intoxicated at the time of death and had enlarged, grossly

TABLE 4

Fat Vacuolation of Liver Cells in 53 Shock Cases Uncomplicated by Major Infection

GRADE OF FAT VACUOLATION	SURVIVAL PERIOD		
	Less than 18 hours	18 to 96 hours	More than 4 days
0	11	3	9
1	2	6	3
2	1	4	4
3	0	9	1
Percent positive.....	22%	87%	47%
Percent grade 2+ or 3+.	8.2%	59%	29%

TABLE 5

Centrolobular Fat Vacuolation of Liver, Control Cases

TYPE OF CASE	NUMBER	GRADE OF FAT VACUOLATION				PERCENT GRADE 2 OR 3
		0	1	2	3	
Sudden deaths.....	17	8	5	2	2	24%
"Medical" deaths.....	15	3	6	3	3	40%
Aplastic anemia.....	20	10	6	1	3	20%
Starvation.....	38	0	0	0	0	0
Shock (less than 18 hours).....	14	11	2	1	0	8.2%
Shock (18 to 96 hours survival)....	22	3	6	4	9	59%

fatty livers suggestive of chronic alcoholism. In contrast, the acute-shock group, with survival periods shorter than 18 hours, was made up almost entirely of battle casualties, all previously healthy and vigorous young men, and therefore represents a better control group than the "sudden" deaths. The relatively high incidence (40 per cent) in the "medical" deaths is not surprising in view of the multiple etiology of fat deposit in the liver, but is well below the 59 per cent frequency in the 18 to 96 hour shock group. The starvation cases provided a most interesting contrast to the shock material. Although fat was present in the majority, it was always manifest at the periphery, never at the center of the lobule.

Summary. Eighteen hours after a shock-producing injury, fat vacuolation was demonstrable in the liver cells at the center of the lobule and was found in 87 per cent of 53 cases uncomplicated by major infection in the period from 18 to 96 hours after injury. It was of moderate or severe grade in 59 per cent. After the fourth day, its frequency and severity diminished.

Kidney. The complex series of changes appearing in the kidney in lower nephron nephrosis have been described repeatedly (3,4,5) with substantial agreement by all authors. They need not be detailed again on this occasion. One phenomenon, however, previously unnoticed or unemphasized in the kidneys of patients who have suffered from shock-producing trauma is the appearance of fat vacuolation in the ascending limbs of Henle's loops. As in the heart and liver, fat vacuolation was rarely found in shock patients surviving less than 18 hours after injury. It was already present in 55 per cent of the 18- to 24-hour

TABLE 6
Fat Vacuolation of Ascending Limbs of Henle in 90 Shock Cases

SURVIVAL PERIOD	NUMBER OF CASES	GRADE OF FAT VACUOLATION				PERCENTAGE POSITIVE	PERCENTAGE GRADE 2+ OR 3+
		0	1	2	3		
Less than 18 hours.....	20	17	2	1	0	15%	5%
18 to 24 hours.....	11	5	1	4	1	55%	45%
24 to 96 hours.....	26	4	1	4	17	85%	81%
More than 4 days.....	33	13	6	7	6	58%	39%

TABLE 7
Fat Vacuolation of Ascending Limbs in 55 Non-shock Cases: Control Group

TYPE OF CASE	NUMBER	GRADE OF FAT VACUOLATION				PERCENTAGE POSITIVE	PERCENTAGE 2+ OR 3+
		0	1	2	3		
Sudden deaths.....	19	19	0	0	0	0	0
"Medical" deaths.....	14	8	3	1	2	43	22
Starvation deaths.....	12	8	1	3	0	50	38
Aplastic anemia.....	10	8	1	1	0	25	13

group and was evident in 85 per cent of those surviving from 1 to 4 days. With survival beyond that period, it decreased somewhat in frequency to 58 per cent, and considerably in severity, the 2+ and 3+ grades dropping from 81 to 39 per cent. In the kidney, as in the heart, the severity of fat vacuolation was uninfluenced by the presence or absence of peritonitis, the only common septic complication in the series. Figures on 90 shock cases are presented in Table 6.

Control Cases. Approximately the same control cases were used as in the previous sections. The degree of fat vacuolation in the ascending limbs in 55 control cases is shown in Table 7.

Fat vacuolation in the ascending limbs of Henle's loops is found with sufficient frequency (43 per cent of the "medical" deaths in the present group) to have led some authors (7) to consider it normal. Its complete absence in 19 cases of sudden death and its presence in only 15 per cent of 20 shock cases sur-

viving less than 18 hours from injury clearly indicate that it is not normal in healthy young men in the 18- to 35-year age group. Dible (8) has shown that fat rapidly appears in this segment of the nephron in starvation experiments in rabbits. The data on starvation deaths included in our series showed an incidence of 50 per cent, with 38 per cent of 2+ or 3+ grade. These figures are nevertheless well below those of the 1 to 4 day shock cases (85 and 81 per cent respectively) shown in Table 6.

Summary. Fat vacuolation of the ascending limbs of Henle's loops is abnormal in men from 18 to 35 years of age. It was present in only 15 per cent of shock patients dying in less than 18 hours but was present in 85 per cent of shock patients surviving from 1 to 4 days after injury. From the fourth day onward, a decrease in severity was demonstrable, regardless of whether a hemoglobinuric nephrosis developed.

TABLE 8

Doubly Refractile Lipids in Adrenal Cortex in 40 Shock Cases without Sepsis and in 18 Cases of Sudden Death

TYPE OF CASE	NUMBER OF CASES	AMOUNT OF LIPID				PERCENTAGE DIMINISHED	PERCENTAGE GREATLY DIMINISHED
		3+	2+	1+	0		
Sudden deaths	18	15	3	0	0	17%	0%
Shock less than 18 hours	11	8	2	1	0	27%	9%
Shock 18 to 96 hours	13	1	4	7	1	92%	61%
Shock more than 4 days	16	3	7	3	3	81%	38%

Adrenal. A normal adrenal gland is rarely seen at necropsy by the civilian pathologist who does not have opportunity to perform postmortem examinations upon individuals who have died suddenly without previous disease. The adrenal gland of the healthy young male has a narrow cortex which ranges from 1.0 to 1.3 mm. in width. The cells are packed with lipid (stainable with Sudan IV), predominantly in the fascicular layer, but numerous vacuoles are also demonstrable in the zona glomerulosa and reticularis. Limited to the zona fasciculata are large amounts of doubly refractile lipid which serve to outline this layer sharply when viewed with crossed Nicol prisms.

In our shock cases, no medullary but a variety of cortical changes were observed. The amount of stainable lipid decreased and the optically active fraction was markedly depleted. The cortex was slightly swollen and frequently showed the pseudo-acinar type of degeneration described and illustrated by F. B. Mallory in 1914 (9) and recently emphasized by Rich (10) in relation to sepsis. The changes did not differ qualitatively from, and were less severe quantitatively than, those of sepsis and of such control conditions as aplastic anemia and starvation, though some degree of terminal infection may have complicated much of this control material. Only one feature, the doubly-refractile lipid depletion, showed evidence of reversibility with recovery from shock. Table 8 shows the amount of doubly-refractile lipid in 40 shock cases, free from septic complications, and a control group of 18 cases of sudden death. As in other organs, the amount of lipid was visually estimated on a 0 to 3+ scale. In this instance, however, the maximal 3+ figure represents the normal and zero the stage of complete depletion.

Doubly refractile lipid was occasionally below the usual level in cases of sudden death and was mildly depleted in 27 per cent of shock patients dying in less than 18 hours, in one

case severely depleted. In the shock cases of 18 to 96 hours' survival, it was diminished in all but one instance (92 per cent of the cases) and markedly so in 8 cases, or 61 per cent. In those patients surviving more than 4 days, some evidence of a tendency to return to normal is shown by a drop in the percentage of severe depletion from 61 to 38 per cent.

Control Material. It was difficult to know what kind of control material would be suitable inasmuch as most types of illness which lead to death produce similar and even more marked adrenal changes. Four groups of control cases are listed in Table 9. It is evident that a wide variety of factors affect the storage of lipid substances in the adrenal cortex, many of them more profoundly than does shock.

COMMENT

A pattern of parenchymal degenerative changes has been described in the heart, liver, kidneys and adrenals of patients who have suffered a shock-produc-

TABLE 9
Doubly Refractile Lipids in Adrenal Cortex in 44 Control Cases

TYPE OF CASE	NUMBER OF CASES	DOUBLY REFRACTILE LIPID	
		Percentage diminished	Percentage greatly diminished
"Medical" deaths	14	79	29
Starvation deaths	9	100	78
Aplastic anemia	11	91	91
Septic deaths	10	100	100

TABLE 10
Percentage of Abnormal Fat Changes in the Heart, Liver, Kidneys and Adrenal in Shock

TYPE OF CASE	HEART	LIVER	KIDNEY	ADRENAL
Sudden death controls	0	24	0	17
Shock, less than 18 hours	0	22	15	27
Shock, 18 to 96 hours	75	87	76	92
Shock, more than 4 days	17	47	58	81

ing injury. Are these in fact consequences of shock? None of the changes described is specific for the state of shock. Fat is known to make its appearance in one or another of these organs in response to a variety of pathologic conditions such as anoxemia, starvation, and chemical or bacterial agents, and lipids disappear from the adrenal cortex under an even greater variety of conditions. Critical examination of the data is therefore necessary before concluding that the observed changes are due to shock.

Errors of subjective interpretation in relying upon such vague changes as "parenchymatous degeneration" and "cloudy swelling", which are readily confused with postmortem degeneration and the artifacts of faulty histologic technic, have been avoided by the use of frozen sections and fat stains. The observed variations from the normal are therefore vital phenomena.

Next in importance are the time relationships to shock. Table 10 shows the percentage of all cases with abnormal fat vacuolation in the heart, liver and kidney, and the depletion of doubly-refractile lipid in the adrenal for three time intervals relative to the shock-producing injury and for the sudden death control group. In each of the four organs studied, no significant difference in demonstrable fat is apparent between the sudden death series and the shock cases in which death occurred in less than 18 hours. Abnormal changes are evident, however, in these organs in from 75 to 92 per cent of shock patients who survived from 18 to 96 hours after injury. The almost synchronous appearance of the lesions 18 hours after injury in all four organs suggests a common causative factor. The delay in appearance of the morphologic evidence of injury in many instances until shock has been relieved is not incompatible with a causal relationship.

Of equal importance in establishing an etiologic relationship between shock and the lesions which have been described is evidence of reversibility, of return to or at least toward normal with increasing intervals after the episode of shock. As all the necropsy material available for this study necessarily derived from

TABLE 11
Incidence of Severe Fatty Changes in Shock Cases
(Percentage of Cases Studied in Each Category)

TYPE OF CASE	HEART	LIVER	KIDNEY	ADRENAL
Shock, 18 to 96 hours' survival	50	59	81	61
Shock, 4 days' or longer survival	12	29	39	38

individuals with lethal disorders, it is not surprising that a complete return to normal was not usually demonstrable. Clear evidence of a tendency to reversibility is shown in Table 11, in which the more severe grades of changes in the 18- to 96-hour group are compared with those in cases surviving 4 days or longer. It is noteworthy that the time interval before recovery is demonstrable is essentially the same in all four organs, the change becoming demonstrable on the fourth day in each instance. The possible contention that the changes described are merely agonal, like depletion of liver glycogen, is refuted by this evidence of reversibility in a large number of cases progressing to a fatal outcome due to other factors.

Though it has been repeatedly stressed that none of the changes described can be considered pathognomonic of shock, it is possible that the *pattern* of changes may be. This is suggested by Table 12. The percentage incidence of the lesions under consideration has been compared in shock patients surviving from 18 to 96 hours with three groups of control cases: a miscellaneous group of "medical" deaths, a group of aplastic anemia fatalities and one of starvation deaths. Only in the shock group do more than three-fourths of the cases show involvement of all four organs.

SHOCK AND LOWER NEPHRON NEPHROSIS

The four lesions described above have been shown to occur in more than three-fourths of all shock cases which come to necropsy in the period from 18 to 96 hours after injury but to be transitory phenomena which disappear within a few days of recovery from the episode of shock. A fifth and far more important lesion, since it is usually irreversible and commonly leads to death from renal insufficiency, appears in a comparatively small proportion of shock cases. It was found in 10 per cent of 1,000 necropsies upon battle casualties who died in Army hospitals during the Italian campaign, but I know of no data which give reliable indication of its frequency in relation to the clinical state of shock. Like the lesions previously described, it is not specific for the state of shock since it is seen in such varied circumstances as transfusion reactions, the crush syndrome, infusion of human hemoglobin, irrigation of the bladder with tap water during a transurethral prostatectomy, mushroom and carbon tetrachloride poisonings, sulfonamide sensitivity, heat stroke, burns, malaria and other conditions. It has been described under many names such as lower nephron nephrosis (3), hemoglobinuric nephrosis (4), traumatic anuria (4), transfusion

TABLE 12
Distribution of Lesions in Control Groups
(Percentage of Cases Studied in Each Category)

TYPE OF CASE	HEART	LIVER	KIDNEY	ADRENAL
Shock, 18 to 96 hours' survival.....	75	87	76	92
Starvation.....	0	0	50	100
Aplastic anemia.....	33	20	25	91
"Medical".....	27	40	43	79

kidney (11) and interstitial nephritis (12). Descriptions of the clinical and pathologic features and discussions of the pathogenesis of the lesion can be found elsewhere (5). It is evident that no single factor can explain the development of the lesion but that shock, heme-pigment excretion in the urine, and drug sensitivity are each important. The only feature germane to our present topic is the relationship of this lesion to the state of shock.

Our attention was drawn early in the Italian campaign to the probable etiologic importance of shock by an analysis of the source of the first 100 cases of pigment nephropathy to pass through the pathology section of the 15th General Laboratory. The lesion was found in only 6 per cent of the necropsies from the Base Section Hospitals, it was present in 18 per cent of fatalities in the Evacuation Hospitals, and the incidence rose to 30 per cent in the Field Hospitals (to which only the most severely wounded, non-transportable cases were admitted). The implication was clear that pigment nephropathy occurred in direct proportion to the severity of injury and, by inference, to the profundity of shock.

More direct evidence was provided by the studies of the previously mentioned Board. In 183 severely wounded individuals, studied by my clinical

colleagues of the Board, data were adequate to permit a classification of the degree of shock in three grades: severe, moderate and slight. In 37 of the 60 cases from this group who died, a pigment nephrosis was demonstrated at necropsy. The distribution of the renal lesion among the various categories of shock is shown in Table 13.

The decreasing frequency of renal involvement as one passes from those with marked shock to those with only slight degrees of shock is apparent, but the six patients who were not considered to be in shock confuse the picture. One of these cases was a frank transfusion accident; 150 cc. of A blood was given to an O recipient before the error was recognized and the transfusion interrupted. Massive hemoglobinuria resulted. Three other cases were examples of the crush syndrome characterized by severe myoglobinuria. Though clinical shock was never apparent, all three cases developed marked hemoconcentration despite intensive intravenous fluid therapy. If these four cases, in which extensive mobilization and excretion of heme pigments, either hemoglobin or myoglobin, dominated the clinical picture, are eliminated, the occurrence of pigment nephrosis in the no-shock category falls to 6 per cent. We may there-

TABLE 13
Incidence of Pigment Nephropathy in Relation to Shock

GRADE OF SHOCK	NUMBER OF CASES	FATAL NEPHROPATHY	PERCENT
Severe	57	20	35.1
Moderate	55	7	12.7
Slight	37	4	10.8
None	34	6	17.6

fore conclude that the frequency of pigment nephrosis closely parallels the severity of shock except where massive mobilization and excretion of heme pigments complicate the situation. Shock is an important but not sole factor in the development of this lesion.

SUMMARY AND CONCLUSIONS

A standard pattern of recognizable changes was found in patients with traumatic shock who survived a minimum of 18 hours after injury. This consisted of fat vacuolation of the myocardium, of the central cells of the liver lobules and of the ascending limbs of Henle's loops in the kidney. In the adrenal gland, the doubly-refractile lipid of the zona fasciculata became depleted after the same time interval. In all four organs, these changes persisted for three days after injury but from the fourth day onward, in cases uncomplicated by infection, a tendency to return to normal could be demonstrated. The incidence of this pattern of changes proved significantly higher in shock cases than in a variety of control material. It was concluded that they constitute evidence of parenchymatous injury produced by shock.

A fifth lesion, named by Lucké lower nephron nephrosis, appears in a smaller

but significant proportion of shock cases. A correlation between the severity of shock and the frequency of this lesion indicates that shock is an important factor in its development.

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AMYOTONIA CONGENITA*

A REPORT OF THREE CASES WITH A REVIEW OF THE LITERATURE

JOSEPH ALLAN EPSTEIN, M.D.

Amyotonia congenita is a rare congenital disease originally described by Oppenheim (1) in 1900 and characterized by profound generalized muscular weakness and atonia. Although more than 200 cases have been reported and approximately 60 of these are accompanied by comprehensive anatomical studies, the interpretation of the pathological anatomy and pathogenesis is still the subject of controversy. This report will add three cases to those described and their clinical and pathological features will be presented and evaluated in the light of recent studies.

CLINICAL FEATURES

Onset. The symptoms of amyotonia in the great majority of patients are manifested at birth or soon thereafter. Faber (2) found this to be true in 81.9 per cent of 115 reported cases. Symptoms which seem to appear spontaneously during the first two months after an acute illness probably existed at birth, and may not have been recognized until accentuated by intercurrent disease (3, 4, 5, 6). One doubts the true character of those cases occurring after a period of good health in infancy (7).

Underdevelopment and hypotonicity of the skeletal musculature makes its appearance in early infancy when it is observed that the child is unable to support its head or sit erect; even in milder forms of this disease these acts are accomplished at an age considerably later than normal. The inability of the infant to express milk from its mother's breasts, as a first manifestation of weakness was observed by the parents in two of the cases reported by Reuben (4). While prenatal movements of a normal or unusually vigorous type are not uncommon, evidence that the condition antedates birth has been offered by Turner (8) who described a family in which all of the six children developing amyotonia congenita failed to exhibit intrauterine movements. Quickening was absent, weak or retarded in 54 per cent of the cases in Faber's group (2). This has been found consistently by others (4, 7, 9). Otherwise, the course of pregnancy is normal (2). The mother's description of the character of fetal movements is of little aid in fixing the date of onset because the vigor of these movements under normal conditions varies greatly in individual cases.

General appearance and muscle status. The child's face lacks the normal mobility of facial expression and possesses no signs of individuality (4). The arms are held in abduction with the elbows flexed and the hands pronated. The thighs are held partly abducted with the knees flexed and the feet rotated outward. The feet are long, flat and pad-like. The pad foot, characterized by the

* From the Neuropathological Division of Laboratories, The Mount Sinai Hospital, New York.

presence of fatty masses on the dorsum, was first described by Collier and Wilson (10) as typical of amyotonia congenita. It is regarded as an uncommon congenital defect and has been observed by others in this condition (2, 4, 6, 11).

Deformities such as lordosis, kyphosis and scoliosis are observed in the sitting position. These defects are the results of hypotonicity during the period of postural development. The musculature of the neck is incapable of maintaining the head erect with the result that the chin falls forward, resting on the sternum. Since respiration is purely diaphragmatic, bilateral compression of the chest results in an increase of the antero-posterior diameter at the expense of the lateral. The abdomen is large and protuberant.

Although the extremities appear symmetrically paralyzed, the condition is actually one of profound weakness. The widespread hypotonia is most evident in the lower extremities and least in the muscles innervated by the cranial nerves. No individual muscle in a group is spared although the muscle groups are seldom affected to the same degree (4). Those which move the proximal joints may appear to be more affected than the distal groups. However, since the former act at a mechanical disadvantage, this discrepancy may be more apparent than real (12). The ability to move the fingers and toes slightly is retained even if power to move the arms, legs, trunk and neck is not present (4). In none of the 77 cases reviewed by Reuben was muscle weakness absent in the lower extremities. In patients under 1 year of age, the muscles of the trunk and neck were invariably affected. The associated lengthening of the ligaments of the joints enables one to place the limbs into bizarre positions which the child is unable to correct (3, 4). Contractures are most frequent in the lower extremities and are the only factors limiting the remarkable positions into which the extremities can be placed (4). As a result of muscle weakness, it is impossible for the child to rise from the recumbent position. In those cases in which partial recovery has occurred, rising is accomplished in the step-ladder fashion characteristic of progressive muscular dystrophy.

The muscles are small and flabby and can be palpated with difficulty, if at all, within the enveloping mass of fatty tissue (3, 13). Only in advanced cases in which the subcutaneous panniculus has been absorbed is the smallness of the muscles recognized.

Of the muscles supplied by the cranial nerves, only those of the face and tongue are definitely affected. The feebleness of the cry and vocalization is probably due more to the child's generalized weakness and the intercostal paralysis than to any disturbance in the laryngeal musculature. Difficulty in swallowing, when encountered, may also be attributed to these dysfunctions (14).

It is significant that the muscles of deglutition, the diaphragm and the sphincters are not involved. The heart and viscera are similarly excluded (2, 7). Thus, those elements necessary to sustain vital processes are preserved.

Signs of malformations and developmental retardation in cases of amyotonia congenita have been described by several authors (2, 4, 15, 16). Such deformities include club foot, dislocation of the hip, shoulder and thumbs, malformation

of the knee, malocclusion of the jaws, deformities of the skull, spina bifida, undescended testicles, and umbilical and inguinal hernias.

Neurological findings. Intelligence was found to be normal by most observers (2, 8, 12). Reuben (4), however, records the mental status as normal in 61 cases and backward in 20. Two were idiots and a small number were noted to be precocious.

The deficiency in facial expression and the lack of muscular activity and tonus have already been described. The deep reflexes are absent in most cases. Faber, however, (2) reported the presence of knee jerks in 26.6 per cent of his cases while Reuben (4) and Burdick, Whipple and Freeman (7) reported them as uniformly absent. As a rule the conjunctival and pharyngeal reflexes are present. The reflex activity does not remain unchanged in all cases. In one case recorded by Faber the knee jerk returned after being absent for a period of five years. Similar findings were reported in six of the cases included in Reuben's series in which improvement was present. In no case was there a disappearance of reflex activity after it had once appeared (4).

The superficial reflexes were reported as normal in 60 per cent and absent in 40 per cent of Reuben's cases (4). Faber (2) recorded the abdominal reflexes present in 50 per cent of the cases reviewed by him. Adequate observations of these reflex responses have not been recorded in the other reports.

Sensory appreciation in the majority of these patients is normal. Most authors have commented on the patient's remarkable tolerance to testing with the faradic stimulating current during muscle evaluation. This phenomenon is considered to be of diagnostic significance.

Laboratory data. The electrical reactions form a distinct pattern in which there is a quantitative diminution of electrical irritability without the qualitative changes characteristic of degeneration. This phenomenon is present in all degrees of intensity varying from a slight diminution in faradic irritability to a complete absence of reaction to both faradic and galvanic stimuli (2, 4, 10). This lack of response is most evident when testing with the faradic current. Like the tendon reflexes, the response is seen to vary with the muscle group tested, those of the face usually showing normal reactions (4). The reaction of degeneration seen in lesions of peripheral nerves and in destructive processes involving the anterior horn cells is never observed (7).

Roentgenographic studies have disclosed evidence only of secondary changes related to muscular dysfunction such as the osseous deformities and medullary thinning characteristic of disuse atrophy (2).

Biochemical studies reveal alterations in the creatine-creatinine metabolism similar to that present in muscular dystrophy. Ziegler and Pearce (17) found a lowered creatinine excretion in a patient kept on a creatinine-free diet. In addition, there was excretion of creatine while on a low protein diet. There was no chemical evidence to indicate breakdown of nucleo-protein or osseous elements.

The presence of blood and urine creatinine values of less than one-half the

normal amount has been explained by the great reduction in creatine metabolism that occurs as a result of the atonia and immobility. Creatinine, a waste product of creatine metabolism, is diminished accordingly. Similar findings have been recorded by other investigators (16, 18, 19).

The results of lumbar puncture recorded in three cases have been reported as normal (4).

Clinical course. The course of the disease was marked by stationary periods, periods of regression and periods of improvement. The majority showed a slow but gradual betterment. Not a single case has ever shown complete recovery. In patients manifesting the symptoms of amyotonia quite suddenly after an acute illness, improvement was usually more rapid than in those whose symptoms were present since early infancy. A minority of patients showed a progressive deterioration without improvement (4). Faber (2) noted improvement in 41 cases of the 117 in his series. It was marked in all but 5 cases. Collier and Holmes (5) cite 1 case in which knee jerks were obtained for the first time at the seventh year and in which the child walked at 9. A second case showed complete recovery of motor power in the upper extremities with improvement in the lower extremities associated with the return of deep reflexes. Strauch (13) attributes the clinical improvement more to an amelioration of function than to a progressive anatomical development. The characteristics of the lesions in the central nervous system, in his opinion, almost excluded the possibility of anatomic restitution.

Most of the patients cannot sit up without support or hold their heads upright before 2 to 4 years of age. The great majority do not learn to walk before 4 to 5 years of age and a normal gait has never been observed in this group. When walking is possible, it is of the waddling, steppage, ataxic variety. If impossible, progress by means of rolling in the long axis of the body has been observed. Reuben (4) found 13 patients able to walk in a group of 77 cases older than 16 months of age.

While the condition is compatible with life in a minority of cases the prognosis for recovery is bad. About 70 per cent of the patients die of intercurrent infection before the age of one year (4). In Faber's series, 80 per cent of the fatal issues were due to pneumonia while 10 per cent were due to bronchitis.

Familial incidence. Contrary to Oppenheim's early impression, the occurrence of amyotonia in more than one member of a family is not rare. The literature contains a large number of reports supporting this claim. Gourse (21) presented 2 cases occurring in identical twins while a triplet, born of the same pregnancy, developed normally. Two children of a family of six reported by Gurdjian (3) and six of a family of thirteen reported by Turner (8) were affected. The familial occurrence of 4 cases of amyotonia prompted Krabbe (21) to represent this syndrome as two diseases, one of which was heredo-familial, conforming to Mendelian laws. Foot's report (9) of three siblings born with amyotonia and similar cases of Reuben (4), Benjamin (22), Shuman (23) and Burdick, Whipple and Freeman (7) add emphasis to the familial nature of the disease.

Macklin (24) in a review of the role of heredity in congenital defects of the

nervous system considered amyotonia congenita a recessive inherited characteristic in the 34 families in her group in which more than one child was affected.

While the chances of a normal child being born of parents having had an afflicted child are good, in those cases where two siblings already have the disease, the outlook is dim (7).

ANATOMICAL FINDINGS

Nervous system. The most constant histological changes in amyotonia congenita were found affecting the entire motor system from the cells of Betz of the motor cortex to the end plates and fibers of the skeletal musculature. The alterations in the central nervous system are most intense in those instances in which the symptoms are manifested early and in which muscle involvement is widespread (4).

On gross examination, no changes are usually evident in the brain, but the cord may be diminished in caliber (16, 25). The pinkish, translucent ventral roots are consistently smaller than normal and do not possess the white, opaque sheen observed in the unaltered dorsal roots. Similar findings are present in the cauda equina. The skeletal muscles are thin, pale and have the appearance of raw pork (9). Only the diaphragm retains its normal appearance.

The changes in the central nervous system are most evident in the deep layers of the cerebral cortex, in several of the cranial nerve nuclei and in the motor cells of the ventral horns of the spinal cord. The alterations in the cytoarchitecture of the cerebral cortex have recently been described by Freeman (26). In 4 cases, he was able to demonstrate identical findings in both the pre- and post-central convolutions. The gray matter was noted to be thinner and less cellular than that of normal controls. This deficiency conspicuously involved the multipolar ganglion cells with particular reference to the giant cells of Betz in the precentral gyrus. The immature columnar arrangement of the neuronal elements persisted in the cortex. The cells themselves were relatively underdeveloped. They retained a pyramidal rather than a polygonal form with prominent vesicular nuclei lacking in chromatin, no definite neurofibrils and few processes. No evidence of degeneration was observed. Spiller (27), Bielschowsky (28) and Reuben (4) have also found a similar deficiency of motor cells in the precentral cortex. Others have been specific in their designation of the cytoarchitectonics as normal (6, 16, 29, 30).

Alterations of a degenerative, non-inflammatory character have been described in the neurons of the cranial nerve nuclei. The hypoglossal nucleus is most often affected, its neurons showing chromatolysis and a reduction in number (5, 25, 29, 31, 32, 33). The nuclei of both the abducens and hypoglossal nerves were involved in Baudouin's case (34). Conel (16, 29) reported these changes without numerical alterations in the nucleus ambiguus and in the nuclei of the oculomotor, trochlear, abducens, facial and auditory nerves. Freeman (26) found a moderate deficiency of multipolar elements in the motor nuclei of the trigeminal, facial and vagus nerves.

The spinal cord changes are marked by the scarceness of neurons in the ventral

gray columns and by the altered appearance of the cells that are present. These alterations are most pronounced in the lumbar enlargement and are characterized by the paucity of cells in the anterior horns, the absence of reactive phenomena and the presence of neurons which are either small, rounded and poor in chromatin or long and fusiform with deeply stained cytoplasm. Greenfield and Stern (31), Conel (16, 29) and Hassin (30) described changes in the cells of this region suggesting stages of axonal reaction extending to complete degeneration and neuronophagia. Hassin (30), in addition, reported evidence of a glial reaction in the ventral gray matter marked by an increase in the number of microglia, oligodendroglia and cytoplasmic astrocytes.

A frequent finding in the ventral gray matter has been the "empty" cell beds, a persistent basketwork of myelinated fibers which is seen around the large multipolar cells in this region. In the normal state, the neuron occupies and fills this space while in amyotonia congenita, this space either remains empty or contains a faint meshwork of glial fibers and occasionally a small dot suggestive of a persistent nucleolus (26, 31).

The cells of Clark's nucleus, those in the intermedio-lateral cell column and those in the dorsal gray columns do not show any abnormalities.

In addition to the reduction in the feltwork of fine, myelinated fibers in the ventral horns, there is a striking decrease in the number of medullated fibers in the ventral roots, an observation that confirms the absence of motor cells in the ventral gray matter. These roots appear to be composed primarily of connective tissue. The fiber tracts in the white columns of the cord are usually well preserved, however, occasional reports are found describing a diminution in the number of myelinated axons in the pyramidal tracts (9, 26).

The peripheral nerves have shown a decrease in the number of myelinated fibers together with increased amounts of connective tissue (2, 4, 6, 9, 31). In isolated cases in which degeneration of nerve cells of the anterior horns was present, the decrease in fibers was associated with degenerative changes and with proliferation of perineural and endoneural connective tissue and an increase in the nuclei of Schwann (13, 27, 32, 35, 36). Other authors, although describing root changes, found no abnormalities in the nerve trunks (7, 26, 30, 38).

Muscle. Absence of post mortem rigidity was noted in many of the cases and was explained by a delayed coagulability of the muscle proteins coincident with the inactivity and metabolic changes characteristic of amyotonia.

The skeletal muscles have been consistently found to exhibit changes which parallel those existing in the spinal cord. While evidence of degeneration was not observed by most authors, alterations in the gross architecture with increased amounts of interstitial fat and connective tissue were described by several (5, 9, 25, 31). Considerable thickening of the blood vessel walls has been recorded by Collier and Holmes who considered it to be the end result of a periarteritis (5). Cross sections of the skeletal musculature displayed a mosaic formed by fibers of varying diameters, the smallest resembling those of the 3 to 6 month old fetus before neurotization has been effected (7, 39). Similar patterns have been de-

scribed in the muscles of the tongue by Tuthill and Levey (33). Characteristically, normal fibers of from 20 to 50 microns in diameter lie in close juxtaposition to fibers of small caliber measuring 3 to 6 microns in diameter. The presence of hypertrophied fibers of diameters up to 150 microns has been reported by Collier and Holmes (5). The longitudinal and cross striations are preserved in both the normal fibers and in those present in miniature. In addition, the condensation of sarcolemma nuclei observed in amyotonia resembles that of the normal fetus.

The involuntary muscular structures do not show these alterations. The only cases in which the diaphragm was affected were those of Foot (9) and Wälle and Hotz (40). The muscle of the heart has been described as of the fetal type in 1 case (34).

Nerve endings have been difficult to demonstrate. The majority of reports state that none were found in the affected musculature (9, 7, 25, 33, 37, 41). In the only ante-mortem study available, specimens of muscle taken by biopsy and stained selectively revealed a few simple nerve endings in cross-striated muscle fibers of normal size. No nerve endings were demonstrated on the small muscle fibers (7). Foot (9) described normal terminals on the large, well preserved muscle fibers which were absent on the smaller ones. Bielschowsky (28) found primitive motor plate endings only on the muscle fibers of normal size. He explained their absence on the small undeveloped fibers as due to the lack of development of ganglion cells in the anterior horns of the spinal cord. These were considered to be so primitive that neither their axons nor their motor endings developed. The absence of atrophic and degenerative changes in the skeletal musculature gave support to this concept. Had neuronal interruption occurred after the terminals were formed, signs of degeneration of the muscle fibers would be present. Sensory endings are apparently well preserved (33).

ETIOLOGY

The literature contains many diverse and often contradictory statements concerning the etiology and pathogenesis of this disease. Oppenheim (1) first believed it to be due to arrested development of skeletal muscle. Marburg (36) and Spiller (27) classified it as a form of chronic infantile poliomyelitis. Gurdjian (3), Councilman and Dunn (37), Batten (42) and Kaumheimer (35) believed that a toxic agent acting on the neuromuscular components was the basic factor. Reuben (4) considered the changes to be the result of a primary abiotrophy of the muscles in the fetal stage with secondary failure of the corresponding anterior horn cells to develop due to deficient stimulus from this source. Turner (8) considered it to be a primary myopathy and neuropathy with retrograde degeneration of the anterior horn cells. Hassin (30) considered the glial changes, satellitosis and neuronophagia in the gray matter of the cord commensurate with a destructive lesion rather than a developmental deficiency. Conel (29) described in great detail the presence of cells in the anterior horns in all stages of axonal reaction extending to complete degeneration. The observations of Foot (9)

were similar. These findings indicating a reaction to disease suggest the presence of a fetal poliomyelitis of the type described by Marburg (36).

The theories involving endocrine dysfunction as elaborated by Smith (43) and Baudouin (34) have never received support. Although variations from the normal have been found in post mortem examinations of the glands of internal secretion, alterations in the thymus gland have received the most attention (37, 43). The lack of consistent findings, however, leaves unsupported any causal relationship between endocrine dysfunction and amyotonia. There is no organ in the body which varies so markedly in size as the thymus gland in infants and the etiological role played by this gland must be evaluated accordingly. Slauck (44) considered the basic factor to be a developmental defect of the anterior horn cells aided by an exogenous element such as an acute infection. Grinker (6) stated that it was not possible to determine whether amyotonia was a developmental defect or a degenerative phenomena and suggested that the latter element must be considered seriously. Tuthill and Levy (33) had the same impression.

Greenfield and Stern (31) considered neuronal changes as representative of a degenerative disease beginning either before birth or within the first year of life. Their clinical observations suggested that the increase in function noted in paralyzed limbs was a result of reeducation rather than reinnervation. Archangelsky and Abrikosoff (46) regarded the cord changes in their case as due partly to an arrest in development and partly as a retrograde change. Forbus and Wolf (39) emphasized the embryonic rather than the postnatal origin of the disease. They believed the lesion to be caused by an injurious agent relatively late in the life of the embryo, explaining the lack of evidence of inflammation by its obliteration during the subsequent development of tissues. Faber (2) considered it to be a congenital hypoplasia of the lower motor neuron with secondary changes in the musculature, the original fault being in the defective germ plasm of reproductively exhausted parents.

The occurrence of amyotonia congenita in identical twins and yet absent from a third child born of the same pregnancy but presumably from a different ovum was reported by Gourse (20). This would rule out the effect of an injurious agent particularly if transmitted through the placenta. The author concurred with Faber and considered it more likely that the abnormality was present in the fertilized ovum and that there was a defect in the germ plasm of one or of both parents.

Holmes (38), noting no evidence of degeneration, inflammation or gliosis anywhere, believed his histological findings to be best explained by the assumption of a delayed or retarded embryological development affecting certain anterior horn cells and certain groups of developing muscle fibers. He was impressed by the striking resemblance of the muscle fibers to embryonal tissue and the absence of parenchymal replacement by adipose or connective tissue. Similar findings reported by Cunningham (45) were interpreted as due to an injury of undetermined nature involving the motor nerve cells prior to the establishment of nervous control over muscular development and maintenance. As a consequence,

only those muscle fibers supplied by remaining normal cells proceeded to full development, the others persisted at the embryonal level. The lack of evidence of muscle degeneration or regeneration supports this concept.

Bielschowsky (28), finding no evidence of fatty degeneration in his studies, excluded the possibility of degeneration as the etiological factor of primary importance. He considered the small ganglion cells found in the ventral gray columns to be neuroblasts. The absence of motor plate endings on the small, embryonal muscle fibers was explained as due to abiogenesis of the anterior horn cells which were so primitive that neither their axons nor their motor endings developed.

Hoffmann (46) first described what he termed "empty beds," namely a basket-work of myelinated fibers around large nerve cells persisting although the cells had disappeared. Kaumheimer (35) found similar empty cell beds in the nucleus of the hypoglossal nerve in his case. Bielschowsky (28) regarded such formations together with the presence of shrunken and sclerotic appearing neurons as suggestive of a progressive degenerative process selectively affecting cells which had been retarded in their development.

The finding of developmental retardation and dysplasias in cases of amyotonia lends support to the classification of this disease with the congenital malformations. In 2 cases reported by Lewey (15), there were congenital extramedullary tumors of the spinal canal and in one, congenital aplastic disease of the cerebral hemispheres and brain stem. Bielschowsky (28) found that in cases of amyotonia the posterior columns, the spinocerebellar tracts and the cerebral white matter were not normally myelinated at the end of the third month of life. Dysplasias, heterotopic ganglion cells and medullary and cortical anomalies were also observed. Malformations outside of the nervous system were described by both Marburg (36) and Bielschowsky (28). Hassin (30) reported the presence of conspicuous heterotopias in the posterior roots, in the ventral columns and in the meninges.

The later work of Burdick, Whipple and Freeman (7) and Freeman (26) confirmed the findings of Bielschowsky and added emphasis to his observations concerning the failure of development of the upper motor neuron, both cell body and corticospinal axon, along with the anterior horn cells.

DIFFERENTIAL DIAGNOSIS

The problem of differentiation between amyotonia congenita and the Werdnig-Hoffmann type of infantile muscular atrophy has been clarified somewhat by Grinker (6) who combined all of the post mortem reports available and concluded that it was valueless to differentiate between the two because with maturity they merged clinically. The selective sites of the pathologic changes were identical as were the findings in the skeletal muscle. A difference was found only in the anterior horn cells. In amyotonia congenita, the process was stationary while in the Werdnig-Hoffmann type, degeneration of the ganglion cells was progressive. The absence of products of degeneration in the former condition,

while suggesting a primary abiotrophy, could be explained by the fact that a destructive process may have existed early in fetal life and had subsequently run its course, leaving no residue. Grinker did not consider it possible to determine whether the changes in amyotonia represented a developmental defect or a degeneration. The fundamental difference between amyotonia and infantile muscular atrophy was believed to be only in the matter of the time at which the ganglion cells were affected. In regard to the unity of the two conditions, Grinker is supported by observations made by Rothman (25), Neumann (47) Greenfield and Stern (31) and Tuthill and Levey (33). Slauck (44) expressed the opinion that amyotonia congenita *is* the Werdnig-Hoffmann type of muscular atrophy. Hassin (30) believed that the differentiation could not be made from the microscopic study unless one were familiar with the clinical picture.

The appearance of the muscle fibers does not correspond to that found in atrophy following peripheral nerve injuries and poliomyelitis in that evidence of degenerative changes and the accumulation of products of cell disintegration are absent. In addition, massive replacement of the muscle elements by fat and connective tissue is not seen. Fibrillations are not observed and the electrical reactions characteristic of injury to the lower motor neuron are not elicited (48). The changes seen in simple atrophy following immobilization, cerebral injury, cachexia and starvation involve the fibers of muscle groups in a uniform manner and do not present the varied picture seen in amyotonia. The marked retardation of bone growth and the development of rarefaction common to all of these conditions is not evidenced in amyotonia.

Amyotonia congenita differs from the myopathies in that the latter are conspicuously familial diseases. No verified case of amyotonia congenita has been reported in a myopathic family. Myopathies are not manifested at birth and they never appear acutely or reach their maximum intensity within a short period. The characteristic muscular flaccidity is not present in myopathy and the local muscular wasting that is marked in myopathy is not present in amyotonia. The course of myopathy is one of progressive muscular weakness, that of amyotonia is usually one of progressive amelioration of symptoms. The slow spreading of the affection from muscle to muscle which characterizes all forms of myopathy is not seen in amyotonia (27). The return of reflex function while recorded in isolated cases of amyotonia (10) never occurs in the myopathies.

TREATMENT

Treatment for the most part has not been specific. Physiotherapy employing massage, exercise and faradic stimulation combined with an augmented vitamin intake has been popular. The use of thyroid extract and stimulants such as epinephrine and strychnine has also been employed without noteworthy results. The use of diets containing large quantities of glycocoll in an attempt to alter the creatine-creatinine metabolism has had no influence on the muscular flaccidity. The use of prostigmine in one of the cases treated by Dieckhoff (18) resulted in temporary improvement. Weinberg (49) reported successful treat-

ment of one case of amyotonia using eschatin, an extract of the adrenal cortex. His rationale was based on the observation that since amyotonia congenita is clinically the opposite of myotonia congenita for which quinine is specific, it should respond to drugs antagonistic in action to quinine.

Bicknell (50) and Stone (51) employed large doses of vitamin E and observed an increase in strength of muscular contraction, followed by the ability to sit up and eventually walk. Although the part played by vitamin E has been obscure, the authors consider it essential for the maintenance of neuromuscular metabolism and development.

While the underlying congenital malformation in the central nervous system is not accessible to therapy, the measures recorded represent attempts to achieve the maximal functional result with the surviving tissues. Since the disease is characterized by improvement, supportive care is essential to achieve the maximal functional state. The use of antibiotics should reduce the number of these patients succumbing to intercurrent infection.

CASE REPORTS

Case 1. History. L. M., a male infant, aged 7 months, was admitted to the hospital with a three and a half month history of progressive inability to move his extremities. This loss of power first affected the lower limbs but it soon involved the upper. Prior to the onset of his present symptoms, his movements were said to have been normal. He had never been able to support his head. Two weeks prior to admission, the patient exhibited difficulty in swallowing: his throat would fill with mucous and coughing spells were frequent. These symptoms increased in severity although the muscular power in his extremities improved after "manipulations" and "electric treatments."

Both parents were 32 years of age. The pregnancy was uneventful and the child received an adequate diet. There was no history of contagious diseases. A former child had died at 7 months of age of Oppenheim's disease. It had not moved since birth.

Examination. The child was well nourished. He breathed with gurgling sounds and lay motionless except for slight movements of the forearms and hands. The throat was filled with a large amount of mucus. Respiration was entirely of the abdominal type. The intercostal muscles retracted with inspiration. The child followed light and objects with his eyes. The upper extremities were markedly paretic. Some voluntary motion could be detected in the fingers. There was a flaccid paralysis of the lower extremities except for weak abductor actions and slight movements at the ankles. There was no movement of the axial musculature. The loss of voluntary motor power was bilateral and symmetrical. There was atonia which was most marked in the proximal muscle groups. Deep and superficial reflexes could not be elicited. The child perceived painful stimuli.

Laboratory data. The cerebrospinal fluid, blood and urine studies revealed no abnormalities. Roentgenograms of the long bones showed normal osseous development. Electroencephalogram revealed a normal record.

Course. The child was unable to take food by mouth because of paralysis of swallowing and gavage was instituted. Aspiration resulted, causing severe respiratory embarrassment. On the fourth hospital day, aspiration recurred and signs of pneumonia were evident. After repeated episodes of apnea the child died on the sixth hospital day.

Necropsy findings. The autopsy was performed twelve hours after death. Rigor mortis was absent. There were large quantities of mucus in the trachea and right main bronchus with an aspiration pneumonia in the right lung. The heart showed no abnormalities. The liver was enlarged and congested. The remaining viscera showed no abnormalities. The musculature of the abdominal wall was thin and very pale. The axial and appendicular muscles were soft, flabby and small.

The brain was of normal weight, size and consistency. The spinal cord showed no gross abnormalities.

Microscopic observations. Cerebral cortex. Sections through the paracentral lobule stained with the Nissl method disclosed a marked paucity of multipolar neurons in layers 3 and 5. The pale, prominent, vesicular nuclei of these cells were conspicuously lacking in chromatin material and occupied the major portion of the cell body. Although numerous large nerve cells were present, there were few large pyramidal cells of Betz. The latter occurred singly for the most part and rarely showed the grouping characteristic of the normal motor cortex (fig. 1A). There was no evidence of inflammation or reactive gliosis. Sections taken from other regions of the agranular and granular cortex showed no abnormalities in cellularity or in cytoarchitecture when compared with normal controls. The basal ganglia and midbrain were normal. At the caudal end of the medulla at the decussation of the pyramids, there was an almost complete absence of large, multipolar nerve cells in the ventral columns. Empty cell beds formed by a basketwork of delicate myelinated fibers were numerous in the ventral gray matter (fig. 2).

Spinal cord sections showed a marked paucity of anterior horn cells. This contrasted sharply with the normal cells seen in the posterior horn, in Clark's column and in the intermediolateral cell column (fig. 3). The usual arrangement of the nerve cells into definite and consistent groups was not present in the ventral gray column. Occasionally, a large normally stained isolated nerve cell was seen in the ventral horns. This was most commonly seen in the lumbar enlargement. The majority of the cells, however, were small and stellate, had few processes and contained little chromatin material. Others were long, fusiform and hyperchromatic. Degenerative changes were not seen. The glia cells and vessels were normal.

Sections of the spinal cord stained for myelin disclosed empty cell baskets most numerous in the ventral gray matter in the cervical and thoracic regions. The anterior roots contained few medullated fibers and contrasted sharply with the well-medullated posterior roots (fig. 4). No abnormalities were noted in myelinization of the pyramidal tracts or in any other portion of the white columns. The great contrast between the paucity of myelinated fibers in the ventral roots as compared to the dorsal was readily seen in sections of the cauda equina. The attenuated roots were composed primarily of supporting tissue, traversed by small numbers of medullated fibers. There was no evidence of degeneration.

Sections of the sympathetic ganglia disclosed no abnormalities. Sections of the sciatic nerve, stained with hematoxylin and eosin and the Davenport silver method, did not appear unusual. The trunk was thickly populated with axis cylinders of varying diameter. Unfortunately, no material was available with which to study the number of myelinated fibers.

Muscle fibers. Sections of the skeletal musculature stained with hematoxylin and eosin disclosed considerable variations in the diameter of the individual fibers from normal to approximately one-third to one-fifth normal. The small fibers were miniatures of the normal, possessing the usual cross and longitudinal striations. Although the nuclei of the sarcolemma appeared to be slightly increased among the miniature fibers, this was not considered to be unusual because of the diminished caliber of the small fibers. On being compared with sections from a 4 month fetus, the resemblance was striking. No fragmentation or evidence of degeneration was seen. There were no alterations suggesting fatty degeneration, infiltration or connective tissue replacement (fig. 5).

Specimens of the tongue disclosed the same characteristics as those described in the skeletal musculature. Fetal, miniature fibers were more numerous. The mosaic pattern formed by the mixture of fibers of normal diameter and those of the fetal type was most conspicuous. There was no thickening of the vascular walls and no evidence of degenerative or infiltrative changes. Section from the involuntary musculature showed no significant alterations.

Comment. The inability of the child to support his head at any time throws doubt in the observation that his symptoms began at 3½ months of age. The

events preceding death are those most often found in amyotonia. The histological findings of profound central nervous system and muscular alterations are in accord with a process of considerably longer duration. The presence of a

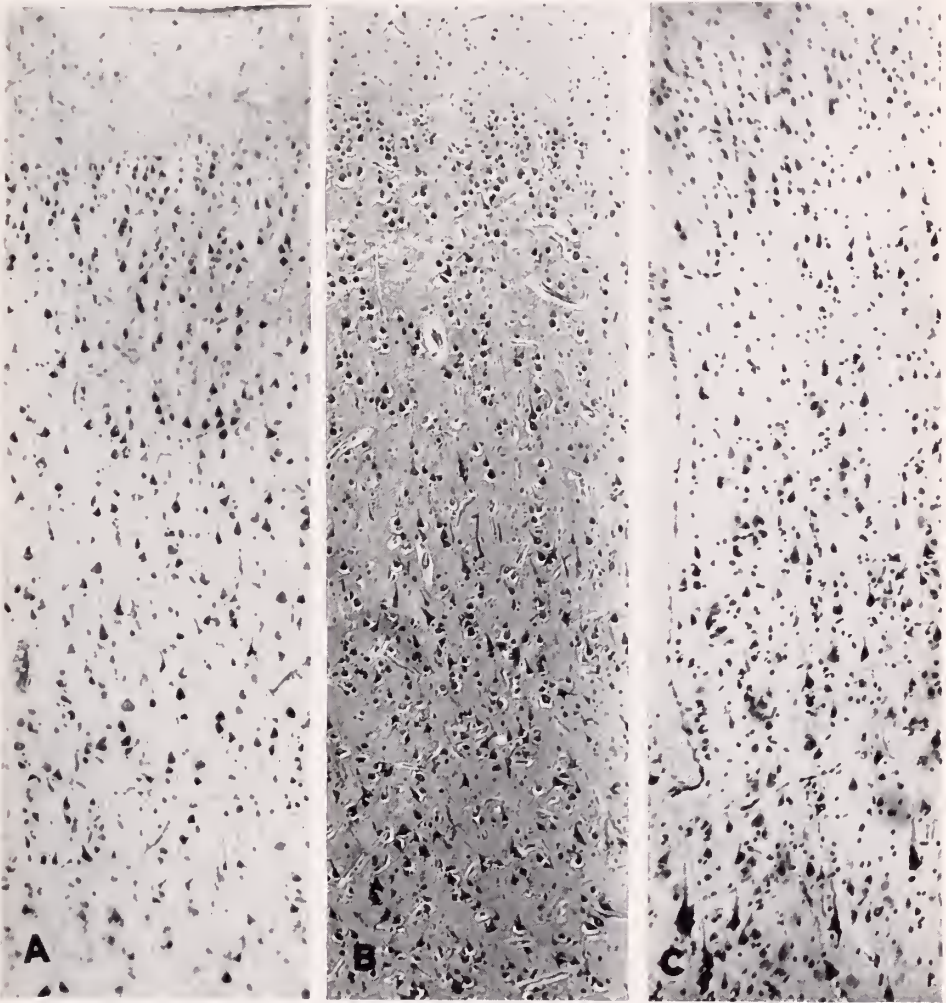


FIG. 1a. Motor cortex (case 1) showing absence of giant pyramidal cells of Betz. The large pyramidal cells in layers 3 and 5 have pale vesicular nuclei with prominent nucleoli and little chromatin material (Nissl stain, $\times 70$).

FIG. 1b. Motor cortex (case 2) showing cellular characteristics similar to those noted in the preceding section (Nissl stain, $\times 70$).

FIG. 1c. Control section, normal brain of 7 month infant, showing the clearly defined cortical lamellation with prominent Betz cells in the fifth layer. The nuclei do not present the immature appearance seen in the preceding sections (Nissl stain, $\times 70$).

sibling dying of a similar condition is not an unusual finding in amyotonia congenita. The symmetrical paresis of the extremities, the atonia, the absence of reflex responses and the retention of sensation were characteristic of this disease. The abdominal type of respiration completed the clinical picture. This is the

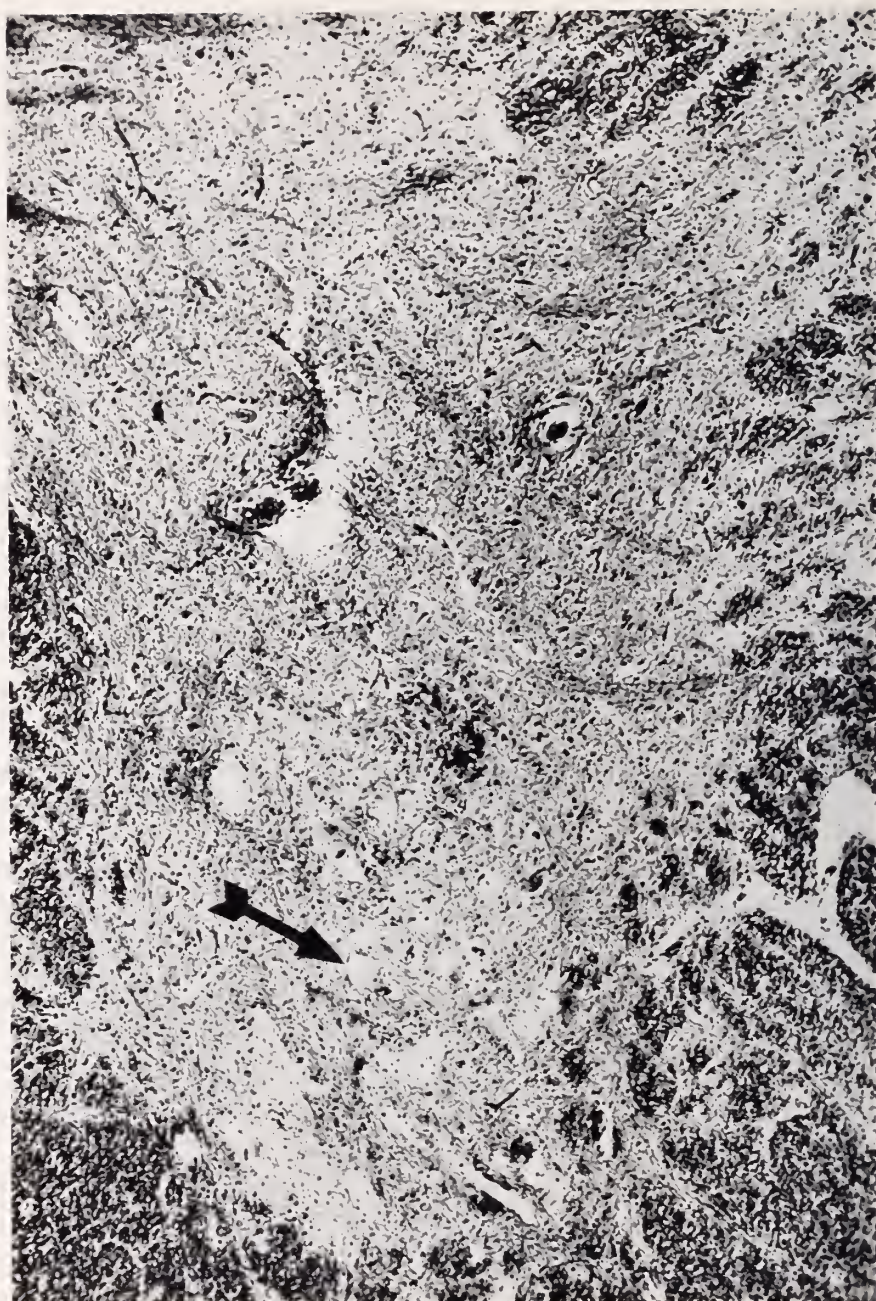


FIG. 2. A section of the lower portion of the medulla (case 1) showing "empty cell beds" formed by a basketwork of delicate myelinated fibers in the ventral gray matter (Weil stain $\times 85$).

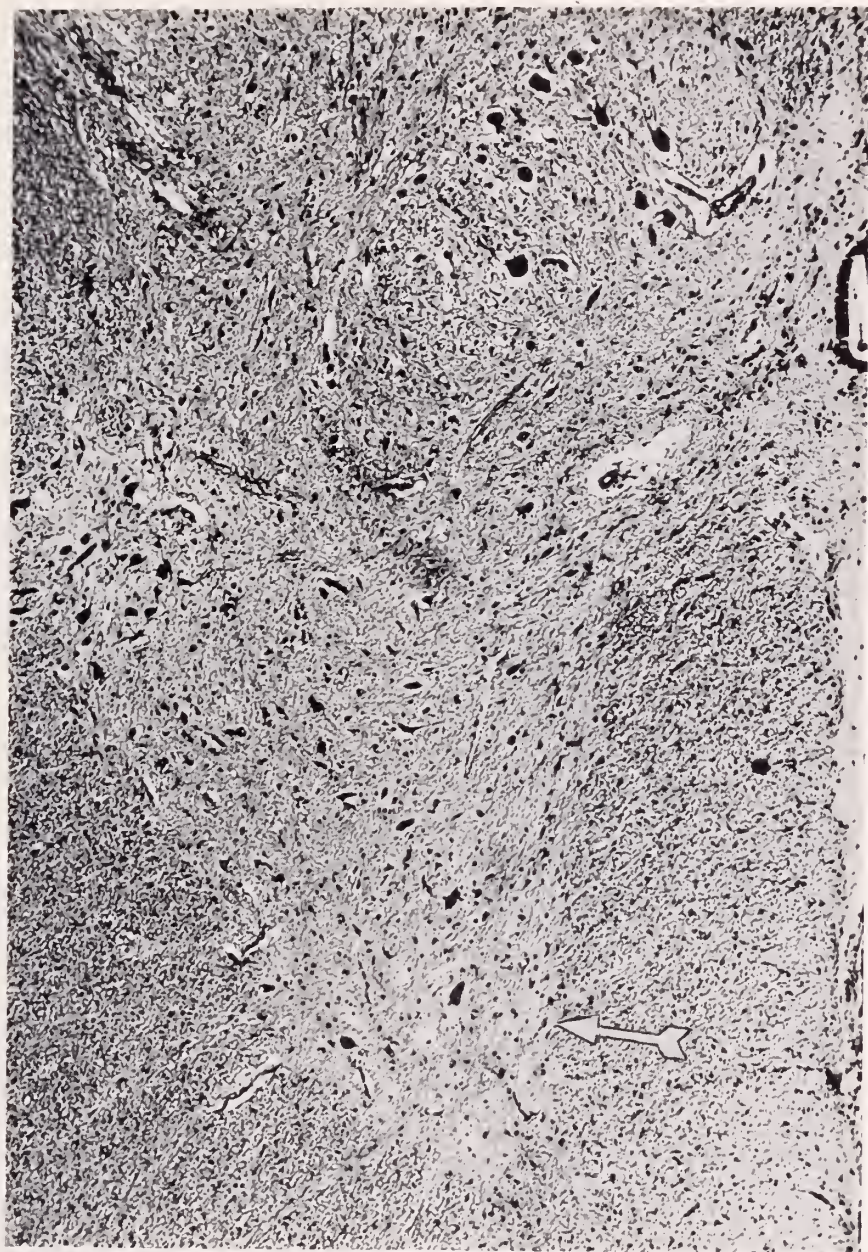


FIG. 3. A section of the spinal cord (case 1) showing the paucity of anterior horn cells (arrow) contrasting sharply with the normal number of cells in the nucleus of Clark and in the intermediolateral cell column (Hematoxylin and eosin, $\times 50$).

only case reported in which an electroencephalogram was taken. The normal record obtained is of no importance in evaluating the cerebral status. Histologically, there was no evidence of degenerative changes in the nuclei of the cranial nerves to explain the difficulty in swallowing. Sections of the tongue disclosed muscular alterations similar to those seen in the skeletal musculature, although not as extensive. Unfortunately, no sections of the other muscles concerned with deglutition were available. The evidence at hand, however, indicates that the swallowing difficulty may well have been caused by both mus-

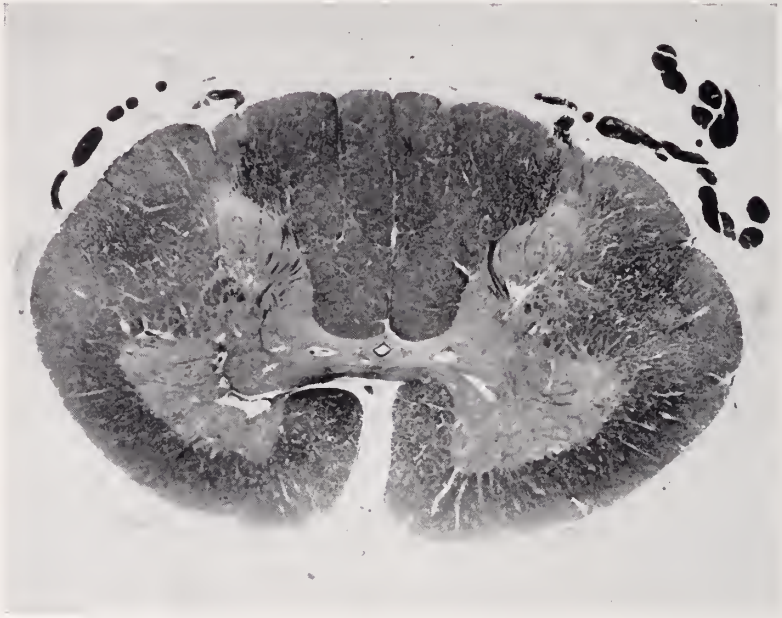


FIG. 4. A section of the cervical spinal cord (case 1) showing the contrast between the normally myelinated dorsal roots and the poorly myelinated ventral roots (Weil stain, $\times 15$).

cular deficiency and profound asthenia. The absence of rigor mortis was a reflection of the generalized atrophy.

The microscopic changes in the cerebral cortex are in accord with those recently described by Freeman (26). The cellular alterations in the cord, the presence of embryonal muscle fibers in juxtaposition with fibers of normal diameter and the absence of signs of degeneration conform to the alterations described by most authors.

Case 2. History. S. G., a male infant aged 3 months, when first admitted was unable to move his arms and legs. At about 3 to 4 weeks of age, the parents first noticed that he would lie without moving for long periods. This change was observed to begin gradually and progress. A remission occurred five weeks after the onset of his symptoms when he was observed to move his hands and arms. Although he could not grasp objects, he stretched his fingers when a doll was presented to him. He was unable to support his head in the erect position. He relapsed into his inactive state one week prior to admission. The child

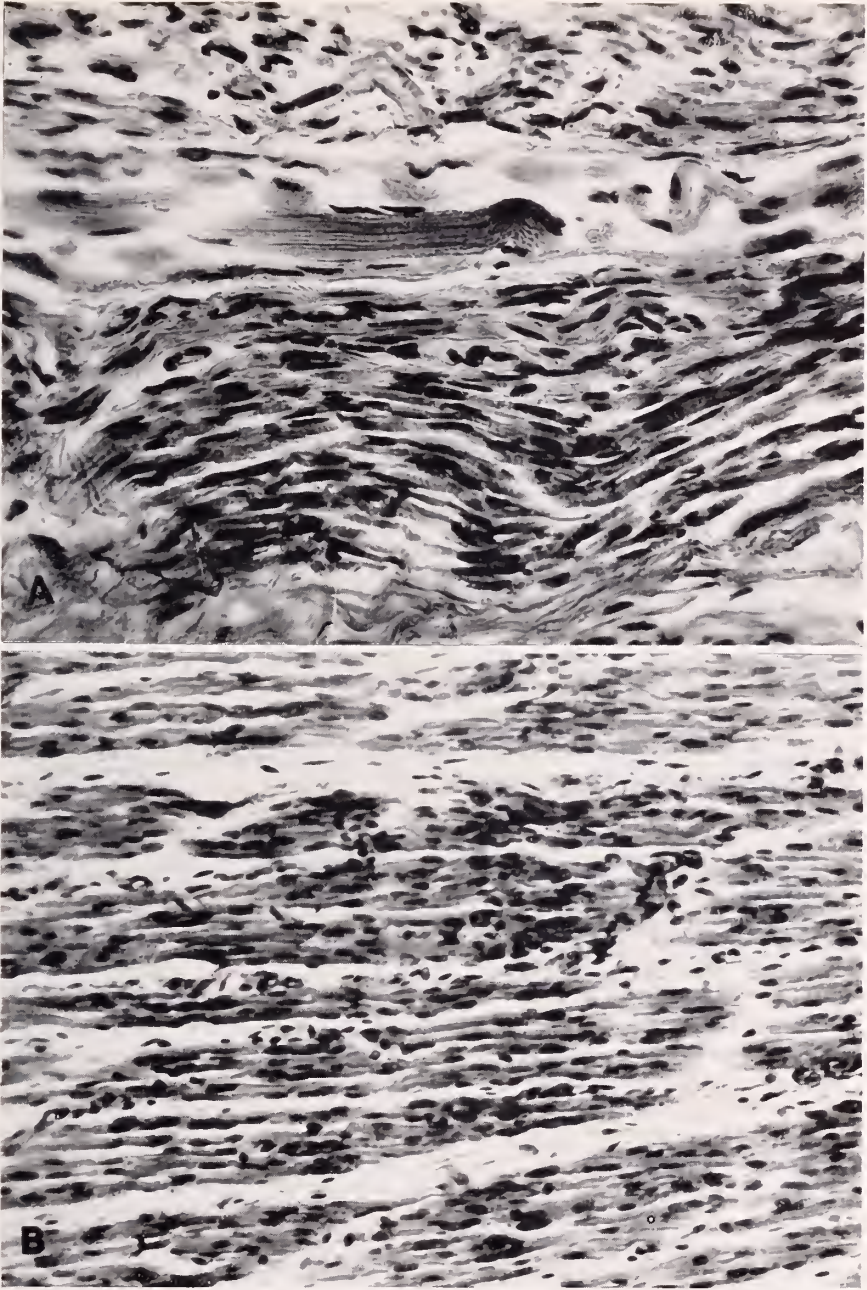


FIG. 5a. A section of the psoas muscle (case 1) showing the differences in the diameter of muscle fibers. Cross striations are seen in both the large fibers and in the small, miniature fibers (Hematoxylin and eosin, $\times 450$).

FIG. 5b. A section of the psoas muscle of a 4 month fetus showing the immature fibers resembling the miniature fibers described above (Hematoxylin and eosin, $\times 450$).

smiled and gurgled at toys, recognized his bottle readily and appeared to be bright and not retarded mentally. He responded to light and to maternal attention.

Examination. The patient was an alert, well developed, fairly well nourished baby lying limp and motionless. The skull was elongated with a posterior protuberance. The sutures and fontanelles were not unusual. The chest was small and thin. Respiration was entirely abdominal. The elbows and wrists could not be completely extended. Examination of the heart, lungs and abdomen was negative.

Neurological examination revealed no abnormalities of the cranial nerves. There was marked flaccidity in the muscles of the neck, trunk and extremities. Those of the face were normal. The head could not be moved or supported. There was slight voluntary movement of the arms, hands, feet and toes. The intercostal muscles were completely paralyzed. No deep or superficial reflexes were elicited. The sensation appeared to be normal. The child hung limply when supported.

Laboratory data. The urine and blood counts were negative. The blood cholesterol was 270 mg. per cent, calcium 11.1 mg. per cent and creatinine 1.1 mg. per cent. Electrical testing revealed that several muscles in the upper and lower extremities did not respond to faradic stimulation. There was a response to strong, interrupted galvanic stimulation. X-rays of the chest were negative. Roentgenograms of the extremities taken prior to admission revealed no abnormalities.

Course. The child's general condition did not change. He took his feedings well and was discharged after two weeks to be followed as an out-patient.

Second admission. History. The child was readmitted at 5 months of age. He had been very weak and apathetic during the interval. During the two weeks prior to hospitalization he took little food and fluid. On the day of admission he developed a high fever and appeared acutely ill.

Examination. The child was extremely dehydrated and toxic. Respiration was rapid and labored, and rib retraction was evident. There was a definite Harrison's groove and slight heading of the ribs. No motion of the chest wall with respiration was observed. Resonance was unimpaired and no râles were heard. The heart sounds were of poor quality. A soft, blowing apical systolic murmur was heard. The rate was rapid and a tic-tac rhythm was present. The abdomen was protuberant and no organs were palpated. Inspection of the extremities revealed a slight widening of the terminal epiphyses without evidence of bowing.

Neurological examination revealed no abnormalities of the cranial nerves. Extra-ocular movements were normal and the pupils reacted to light and accommodation. There was a generalized hypotonia, more marked in the lower extremities. No reflexes were elicited.

Laboratory data. On admission, the hemoglobin was 82 per cent; red blood cells, 4,700,000; white blood cells, 20,000 with 79 per cent polymorphonuclear neutrophils, 18 per cent lymphocytes and 3 per cent monocytes. The urine was opaque and contained albumin, acetone and amorphous phosphates. Blood calcium was 11.6 mg. per cent, phosphorus 6.3 mg. per cent and sugar 170 mg. per cent.

Course. The child was immediately placed in an oxygen tent and given intravenous saline and glucose. He failed to respond and ceased six hours after admission.

Necropsy findings. The autopsy was performed 6½ hours after death. The body was that of a fairly well nourished, poorly developed child. Rigor mortis was slight. There was a hypoplasia of the pectoral, abdominal and axial musculature. Examination of the lungs revealed diffuse signs of atelectasis and bronchopneumonia. The myocardium was uniformly red-brown, firm and of the usual thickness. The remainder of the gross examination was not unusual except for the presence of a hydrocele on the right. No further observations on the appearance of the musculature were recorded although portions of the abdominal musculature and psoas muscle were taken for microscopic study.

Examination of the cranial contents revealed engorgement of the superficial cerebral vessels and a slight prominence of the gyri and sulci. The cerebral hemispheres were

firmer than normally observed at this age. On sectioning the brain, no abnormalities were found.

Microscopic observations. Sections through the paracentral lobule stained with hematoxylin and eosin and the Nissl method revealed a normal number of multipolar ganglion cells. The occasional large pyramidal cells that were present in the fifth layer, although conforming to the shape of the Betz cells, were somewhat smaller in size when compared to those seen in control sections. The greater number of neurons present were oval or roughly pyramidal in shape and possessed prominent, pale vesicular nuclei surrounded by a thin rim of cytoplasm which was drawn out into one or two low, broad-based processes (fig. 1B). Sections taken from the inferior frontal gyrus and insula and portions of the granular cortex disclosed no abnormalities in cytoarchitecture. There were no signs of degenerative changes or gliosis. No alterations of significance were found in the remaining portions of the brain except for the presence of occasional cells undergoing chromatolysis in the nucleus of the trochlear nerve and in the mesencephalic nucleus of the trigeminal nerve. The cells in the nucleus of the hypoglossal nerve were smaller than those of the control cases, possessed fewer processes and little or no tigroid material. The nuclei were large, pale and vesicular and comprised an unusually large proportion of the cell body.

The spinal cord studied at all levels showed that the large multipolar elements were almost completely absent from the anterior gray columns. The majority of those present were small and shrunken. They were heavily stained, poor in chromatin material and possessed few processes. The neurons in Clark's nucleus and in the intermediolateral columns showed no abnormalities. Sections stained for myelin revealed no signs of the empty cell baskets observed in the previous case. The paucity of myelinated fibers in the ventral roots was striking when compared with the dorsal roots.

Muscle fibers. Sections of the diaphragm disclosed no abnormalities. Preparations from the psoas and abdominal musculature disclosed the embryonic characteristics and variation in fiber diameter previously described. There was no evidence of degeneration or of fatty infiltration. In sections of the psoas muscle, special stains (Mallory, Gömöri) disclosed increased amounts of connective tissue in those regions composed predominately of embryonic fibers. This was evident both among the individual fibers and around the muscle bundles and was not observed elsewhere.

Comment. The child presented the usual atonia, areflexia and immobility. The responsiveness of the child and the absence of evidence of mental retardation are characteristic of amyotonia. The creatinine value was normal, an unusual finding in this condition. Testing for electrical responses demonstrated the remarkable tolerance these patients show to the faradic stimulating current, a feature of diagnostic significance. The reactions elicited were not those associated with denervations.

Death followed an acute febrile illness. As in the first case, rigor mortis was not present as usually seen in infants dying in hyperpyrexia. Again, the hypotonia and the lack of activity was the probable cause of this lack of rigidity. The microscopic findings in the central nervous system, peripheral nerves and muscles were similar to those described in the first case. The evidence of cells undergoing chromatolysis in the nucleus of the trochlear nerve and in the mesencephalic nucleus of the trigeminal nerve were probably related to the hyperpyrexia. The absence of signs of reaction about these cells and in regions where pathological changes were evident makes it impossible to accept the alterations as secondary to a specific inflammatory or degenerative disease. The neurons in the deeper cortical layers and in the nucleus of the hypoglossal nerve resembled

neuroblasts. Similar cells were observed in the preceding case, both in the cortex and in the ventral columns of the spinal cord.

Case 3. History. I. C., a female child, aged 21 months, developed normally up to the age of 4 months. Thereafter, development was retarded. She had never been able to support her head, sit or walk. While she had been able to move her upper extremities slightly, movements could be barely elicited in her lower extremities. The child was able to talk without difficulty and no evidence of mental impairment was observed. An older sibling was normal and the parents were alive and well.

About ten days prior to hospitalization, she developed an upper respiratory infection. She was admitted following an exacerbation of her symptoms manifested by a severe cough, respiratory distress and cyanosis.

Examination. The patient was malnourished, appearing ill. She was markedly dyspneic and cyanotic. Respirations were labored and rapid. There was marked frontal bossing of the skull. The fontanelles were closed and no evidence of craniotabes was found. The chest was of the funnel type and the sternum was markedly sunken. The lower ribs flared outwards. Hyperresonance was found over both lung fields except over the area of the right upper lobe where dullness was present. Coarse ronchi and dry râles were heard over the entire thorax. Examination of the heart and abdomen revealed nothing unusual.

The child was unable to raise her head or support it in the erect position. There was marked flaccidity of the lower extremities, more profound than in the upper limbs. Motor power was diminished in all extremities, more prominently in the lower where voluntary movement was not perceptible. All of the joints were hyperextensible. No reflex responses were elicited, either superficial or deep. Sensation was intact.

Laboratory data. Blood study revealed a hemoglobin of 76 per cent and a white count of 17,500 of which 40 per cent were polymorphonuclear neutrophils, 11 per cent were non-segmented neutrophils, 3 per cent were myelocytes, 33 per cent were lymphocytes and 13 per cent were monocytes. Urine analysis revealed 1 plus albumin. Analyses of the blood revealed a urea nitrogen of 7 mg. per cent; sugar, 195 mg. per cent, calcium, 9.3 mg. per cent; alkaline phosphatase, 10 King Armstrong units /100 cc.

A roentgenogram of the chest showed a disseminated bronchopneumonic infiltration of both lungs. Examination of the long bones revealed no abnormalities.

Course. The patient failed to respond to therapy. She ceased on the third hospital day despite intravenous and intramuscular penicillin, oxygen and parenteral fluids.

Necropsy findings. Autopsy was performed eighteen hours after death. The body was that of an emaciated, dehydrated child. Rigor mortis was absent. The head appeared to be enlarged in its antero-posterior diameter. The frontal and parietal bosses were prominent. The sternum was depressed. This was most evident in its lower third. There was a mild flare of the lower ribs. The muscles of the arms and calves were atrophic. The musculature was relaxed and abnormally free movements were elicited in all joints.

Examination of the viscera revealed no abnormalities except for the presence of bronchopneumonia, atelectasis and subpleural hemorrhages in the lungs.

The voluntary muscles were poorly developed. On sectioning, they were markedly pale and muscle bundles frequently appeared to be separated by fatty and fibrous tissue. This was most evident in the gastrocnemius muscle and also in the sternohyoid, intercostal, abdominal and psoas muscles. The diaphragm, however, was well developed and bright pink in color.

The brain was voluminous and otherwise showed no significant alterations. The convolitional pattern was normal. On sectioning the brain, a slight increase in the size of the ventricles was observed.

Microscopic observations. Sections taken from the precentral gyrus in the region of the precentral lobule disclosed numerous medium and large pyramidal cells but extremely rare

giant cells of Betz. The cytoarchitecture was otherwise not unusual in this region or in the sections of the granular cortex examined. Evidence of degeneration or glial reaction was lacking. The basal ganglia, hypothalamus and brain stem were normal.

The spinal cord exhibited small ventral gray columns containing remarkably few normal nerve cells. The majority of the neurons were small, stellate or fusiform, stained deeply and contained little chromatin material. The grouping usually seen in the anterior columns was lacking. There were no signs of reaction. Sections stained for myelin disclosed fairly prominent empty cell baskets in the lumbar segment. The paucity of medullated fibers in the ventral roots contrasted sharply with the richly myelinated fibers in the dorsal roots. This contrast was present, although less evident, in the roots of the cauda equina. Of the striated muscles studied, the diaphragm was the only organ to retain its normal structure. Sections of the rectus, internal oblique, intercostal, psoas and sternomastoid muscles disclosed the mosaic pattern and the small, embryonic muscle fibers previously described. For the most part, these miniature fibers were congregated into discrete groups, however, areas were observed in which they mingled with fibers of normal or greater than normal diameter. Connective tissue stains revealed a slight increase in the connective tissues separating the muscle bundles but not between the individual fibers of the spindles. Sections of smooth and cardiac muscle disclosed no abnormalities.

Comment. As in the preceding cases, this child manifested the profound flaccidity and immobility, more evident in the lower extremities than in the upper. She showed no response to therapy, including penicillin. The absence of rigor mortis and the other findings at necropsy were similar to those observed in the first two cases. Histological studies disclosed rare giant pyramidal cells of Betz in the precentral convolution. The cytoarchitectonics were otherwise not unusual. In this respect, this case differs from those previously described, however, the deficiency of Betz cells still conforms to the observations of Freeman. Unfortunately, additional material was not available with which to further study this critical region. The findings in the cord and muscles were typical of amyotonia. The diaphragm, as in the other cases, presented no abnormalities.

DISCUSSION

The absence of signs of inflammation or degeneration and the observations of immature cells of the neuroblast variety in the ventral horns of the spinal cord and in the third and fifth layers of the precentral cortex, both in the cases presented and in others found in the literature (7, 26, 28) points to a failure of development and maturation as the etiology of this disease. Rather than relating the signs of degeneration in the neurons and muscles described by competent observers to the primary disease, such findings are interpreted as being secondary to the profound systemic infections and intoxications which terminate the course of this illness.

The presence of amyotonia in two of triplets with the third being born in a normal state (20) makes it difficult to accept the theory of Forbus (38) that the pathological findings are due to an intrauterine injurious agent as all three would have been thereby affected. For this same reason, the theories concerning infection must also be regarded with doubt. While the lack of a progressive glial reaction and the absence of neurons are cited in favor of the theory of an aplasia or defective anlage one should, however, be aware of the fact that in the embry-

onic central nervous system, such glial reaction and fibrous scar formation may be completely absent and that a lesion may heal without leaving any histological traces (52).

The theory postulating the occurrence of a premature halt in the process of neuronal and muscular development has been supported by the most convincing evidence. The lack of signs of degeneration, inflammation or gliosis may most adequately be explained by a developmental deficiency occurring in intrauterine life and affecting the cellular components of the voluntary motor system before neurotization of the skeletal musculature had been established.

The development of skeletal muscle in the fetus and the relation of nerve supply to growth and differentiation has been carefully studied. Harrison (53) first demonstrated that the innervation of a muscle played no part in its morphogenesis. This was accomplished by resecting the medullary tube and ganglion crest in tadpoles before histological differentiation into the musculature or the peripheral nerves had begun, thereby eliminating all chance of any peculiar formative stimulus emanating from the nervous system. Despite such precautions, differentiation of the contractile substance was observed to occur in a normal manner.

In the pig embryo, the musculature is differentiated to a considerable extent before the nerve establishes a connection with it (54, 55). At a later period, the muscle becomes dependent on the nervous system for its continued normal existence either through the effects of functional activity or through trophic influences. The work of Caujuno (55) demonstrated that the extrafusal fibers supplied by motor endings change after birth, their diameter greatly surpassing that of the other elements of the neuromuscular spindle. Since multiplication of muscle fibers ceases a short time after birth, the increase in volume of skeletal muscle with activity depends on the enlargement of already existing fibers through an increase in the sarcoplasm and not in the number of fibrils (56, 57, 58).

The differentiation of muscle in the human fetus is apparent at the end of the third month, when both cross and longitudinal striations are apparent (56). The muscle spindles which are proprioceptive in function can be distinguished at about the twelfth week of gestation. In a later period when muscle fibers have differentiated more completely and primitive motor and nerve endings have appeared, the stage of function manifested by contractility appears.

There is no conclusive evidence to show that a muscle without proper innervation can advance in its development beyond a point where its fibers could still be recognized as of late embryonic type. It is this stage of development which is represented in the muscles in cases of amyotonia congenita. The experimental findings recorded above explain the alterations in the musculature in amyotonia as due to the failure of development of the motor innervation in fetal life rather than to a destructive process acting on already formed neuromuscular components in post-natal life. The mixture of normal and embryonal fibers in the same muscle bundle may be explained by relating the former to the survival or maturation of normal anterior horn cells and the latter to the absence of development of motor cells or to the lack of maturation of such cells in the ventral horns.

The estimated proportion of normal muscle fibers to the number of normal anterior horn cells is in accord with this idea. The variety of findings in the peripheral nerves cannot be evaluated insofar as accurately controlled fiber counts have never been carried out. The myelinated fibers with cells of origin in the dorsal root ganglion may mask the microscopic picture in the peripheral nerve, making it difficult to establish a valid comparison with control nerves unless fiber diameters are considered as well.

In evaluating the observations concerning the paucity of the giant cells of Betz in the motor area of the cerebral cortex, one must be aware of the normal distribution of these cells. They are largest and most numerous in the anterior portion of the paracentral lobule and in the dorsal part of the precentral gyrus close to the median longitudinal fissure. Ventrally, their number rapidly decreases and they have already disappeared at the level of the second frontal furrow, especially from the crown of the precentral gyrus (59). Until blocks taken from identical areas are employed uniformly in all cases of comparison studies, the validity of these findings must be observed with caution.

SUMMARY

Three cases of amyotonia congenita are presented and the clinical and pathological features of this disease are reviewed. The findings indicate that there is a congenital deficiency of the entire motor apparatus from the cells of Betz of the precentral convolution to the motor end plates and striated muscle fibers of the effector mechanism. The essential pathological features include a diminution in the number of pyramidal cells in the third and fifth layers of the precentral gyrus, including an absence or marked reduction in number of the giant cells of Betz. The usual grouping of the neurons in the ventral horns is absent and the cells there are few, persisting only as occasional, small, stellate, deeply staining elements with few processes. Cells resembling neuroblasts are present in both the cortex and in the nuclei of the medulla and pons. The ventral roots are deficient in medullated fibers when compared with the normal number of myelinated fibers in the dorsal roots. This discrepancy is further evidenced in the cauda equina. Motor end plates are present only on the muscle fibers of normal size and have never been observed on the small, embryonic fibers which form the outstanding pathological feature of the voluntary muscles. The diaphragm is the only striated muscle to retain its normal appearance. Together with the absence of evidence of degeneration, inflammation or gliosis, these findings suggest that the syndrome of amyotonia congenita is due to a failure of development and maturation of the voluntary motor components of the central nervous system before neurotization of the skeletal musculature has been established.

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TUBERCULOMA OF THE BRAIN ASSOCIATED WITH SICKLE CELL ANEMIA*

PHILIP S. BERGMAN, M.D. AND ROBERT M. BERNE, M.D.

The clinical diagnosis of intracranial tuberculoma is difficult. Wilson, Rupp and Bartle (1), reviewing autopsy material from the Philadelphia General Hospital, found that in only one out of 80 patients was such a diagnosis made correctly. In a patient afflicted, in addition, with some other disease which in turn provokes neurologic manifestations, the diagnostic problem is even further complicated. Such was the situation in the case to be recorded.

CASE REPORT

History. A colored woman, aged 31 years, entered the Mount Sinai Hospital for the last time on January 6, 1948. This was her fourteenth admission in the course of her terminal five years of life.

She was first seen at this hospital in 1942, complaining of a granulating lesion of the vulva of five years' duration. Donovan bodies were demonstrated and a diagnosis of granuloma inguinale was made. She also had had an ulcer on the right ankle for the past 8 years. Blood studies indicated that she had sickle cell anemia.

Since her first admission she returned to the hospital repeatedly for transfusions and local treatment of the ankle ulcer, as well as for the care of the granuloma inguinale. Antibiotics yielded only temporary healing of the ulcer, while tartar emetic, fuadin and streptomycin had little effect on the granuloma.

She received two blood transfusions on October 15 and 16, 1946. On the evening of October 18, after leaving the hospital, the patient noted a burning sensation in the left forearm, had a convulsive seizure, and then lost consciousness for 12 hours; her temperature rose to 101°F. On careful investigation it was determined that this was the first episode of its kind. An almost identical series of events followed a series of two blood transfusions 8 months later (May 24 and 25, 1947). They were considered as transfusion reactions by her physician.

In August, 1947, she reentered the hospital for transfusions. Her heart was found to be enlarged to the left and a rough, loud systolic murmur was heard over the entire precordium, loudest at the pulmonic area; there was also a soft, blowing, pulmonic diastolic murmur. The blood pressure was 114 systolic and 50 diastolic. A sharp liver edge was felt at the level of the umbilicus; the spleen was not palpable. Granulomatous ulcerations had replaced the skin of the entire vulva. There was a large ulcer over the right external malleolus. There were no objective neurologic findings.

Laboratory studies showed a hemoglobin of 5.4 Gm.; red blood cells, 1.8 million; white blood cells 12,000, with a normal differential count. Marked sickling of the red cells was noted on the smear, with a great deal of polychromatophilia and 16 normoblasts per 100 white blood cells. The urine contained a trace of albumin and many white cells. Sedimentation rate (Westergren) was 5 mm. per hour, but differential sedimentation rates, by the method of Winsor and Burch (2), gave a difference of 21 mm. per hour (stased venous blood, 2 mm. per hour; oxygenated blood, 23 mm. per hour). Blood chemical studies showed an icterus index of 2; bilirubin, 0.3 mg. per cent; Van den Bergh, negative; total protein, 7.4 Gm. per cent; alkaline phosphatase, 26 King-Armstrong units; thymol turbidity, 4 plus;

* From the Second Medical Service (Dr. I. Snapper) and the Neuropathology Laboratory of the Mount Sinai Hospital, New York.

cephalin flocculation, 2 plus; urea nitrogen, 17 mg. per cent. A Congo red test showed 35 per cent retention. The blood Wassermann reaction was negative, as were blood cultures. An electrocardiogram showed low T-waves in all leads. The lungs were normal on x-ray studies, but the heart was enlarged, chiefly in the region of the left ventricle. Films of the long bones and pelvis showed an osteochondroma of the left fibula, in addition to generalized coarsening of the trabecular pattern. Thickening and mottling of both tables of the skull were noted.

She was again given two 500 cc. blood transfusions (August 21 and 22, 1947). The second transfusion was immediately followed by a slight rise in temperature. The next day she had a series of Jacksonian convulsive seizures. They began in the left arm, rapidly became generalized, were accompanied by loss of consciousness, and had to be terminated by the administration of sodium amytal intravenously. As she regained consciousness, she was subjected to a complete neurological examination, and the only positive finding was a slightly larger left pupil which reacted more briskly to light.¹ She recalled that shortly before the attack she experienced a feeling of warmth in her hands, and added that these convulsions were identical with those she had had following previous blood transfusions. A lumbar puncture yielded clear cerebrospinal fluid under normal pressure, with a total protein of 20 mg. per cent, sugar 55 mg. per cent and chlorides 743 mg. per cent. The Wassermann and colloidal gold reactions were negative.

Blood transfusions (500 cc. each time), repeated on August 28, 29, 30 and 31, gave rise to another attack. While receiving the last transfusion she developed several generalized (not Jacksonian this time) clonic convulsions, ushered in by a high-pitched cry. The eyes deviated to the left and downward. She lost consciousness and became incontinent of urine. Each seizure lasted a few minutes and between them she would relax but not regain consciousness; they were finally stopped by giving intravenous sodium amytal. Four days after this episode, an electroencephalogram was taken and showed a large amount of diffuse, but not symmetrical, 4 to 6 per second activity. Three per second activity appeared more at the right parietal and occipital than at the other electrodes.

She remained quite well following the last attack and received no intravenous fluids for the next six days. On September 6 she was given 350 cc. of normal saline to test the role of the blood in the convulsive seizures. The next day she had another generalized convulsion which ended spontaneously. She then received six blood transfusions (on September 25, 27 and 30, and October 18, 21 and 24) without any reaction. During this time, however, she complained of intermittent burning sensations in her left hand, usually lasting about five minutes and similar to sensations noted following transfusions given during the previous year. The patient was discharged five days after the last transfusion.

She was readmitted three months later (January, 1948) complaining of progressively severe frontal headache of 10 days' duration. With this she also experienced fever, nausea, anorexia and vomiting. After some injection given by her physician to relieve the headache, she became drowsy and confused, and was brought to the hospital.

Examination. The patient was somnolent and disoriented, with a temperature of 102°F. There was marked stiffness of the neck, but the Kernig and Brudzinski signs were not elicited. The left abdominal reflexes could not be obtained. There were no other positive neurological findings and no new general physical abnormalities.

Laboratory data. Hemoglobin, 9.1 Gm.; red blood cells, 2.9 million; white blood cells, 25,000, with 62 per cent segmented and 9 per cent non-segmented neutrophils, 14 per cent lymphocytes and 15 per cent monocytes. The smear showed extensive sickling and many normoblasts. The spinal fluid was under a pressure of 340 mm. and contained 660 white cells per cubic mm., almost all of them lymphocytes. The total protein was 500 mg. per cent, sugar 20 mg. per cent and chlorides 613 mg. per cent.

Course. The patient remained completely disoriented and often maniacal, requiring

¹ It is not improbable that the emphasis should have been put on a smaller right pupil reacting poorly to light.

heavy sedation. In view of the pleocytosis in the cerebrospinal fluid and other clinical features, the diagnosis of tuberculous meningitis seemed probable, although the possibility of multiple cerebral thrombosis, frequently observed in sickle cell anemia, had to be considered. On the fourth hospital day acid-fast bacilli were identified in a concentrated specimen of cerebrospinal fluid. The patient's condition rapidly became worse, and she died 4 days after admission.

Necropsy findings. General. Miliary tubercles are scattered throughout the lungs, liver and lymph nodes. The spleen is very small and fibrotic, weighing only 2 Gm. The heart displays focal fibrosis and cellular infiltration of the myocardium. In the genitalia there is extensive granuloma inguinale and a right tubal abscess with nonspecific acute and chronic inflammation. The bone marrow is hyperplastic, but no necrosis can be found. Considerable hemosiderin deposition is evident in the liver.

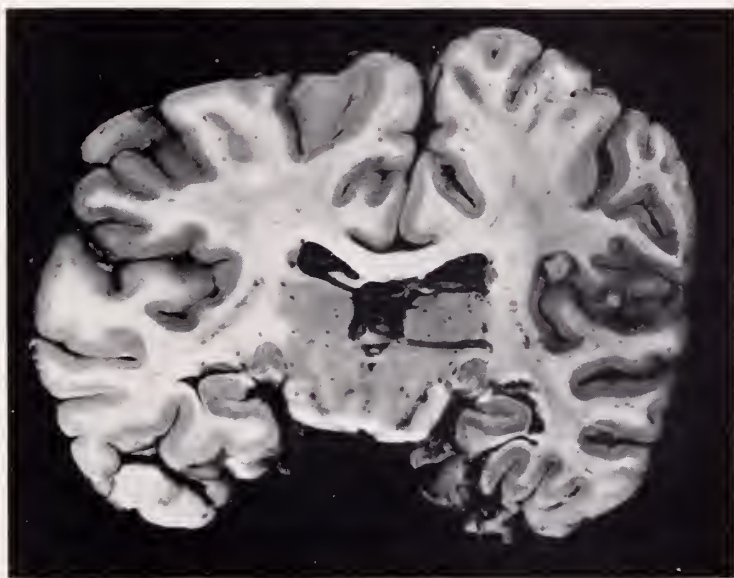


FIG. 1. Coronal section of the brain at the level of the geniculate bodies. The tuberculoma and a smaller tubercle are seen in the cortex lining the depths of the right lateral fissure.

Brain. Gross. It is quite voluminous and shows some asymmetry of the cerebral hemispheres; the right is larger and shows flattening of the gyri with a corresponding reduction in width of the intervening sulci. The right lateral fissure and its ascending ramus display a few small, whitish, opaque, tubercle-like structures. On sectioning, a number of round, well-defined nodules are revealed in the posterior end of the lateral fissure and its branches. These are yellow-gray in color, with cheesy centers, and range in size from 3 to 8 mm. in diameter. The largest occupies the superior and posterior aspect of the circular sulcus, at the level of the geniculate bodies (fig. 1). The meninges are thickened and opaque and display occasional tubercles. There is considerable whitish exudate over the meninges, especially at the base.

Microscopic observations. Sections taken through the region of the lateral fissure show one large, necrotic tubercle and many smaller tubercles of miliary size. Surrounding these there is a ring of fibrous tissue interspersed with lymphocytes, epithelioid cells and Langhans' giant cells. In the cerebral tissue outside this fibrous ring there is moderate glial proliferation. The blood vessels in this region display extensive alterations, with lympho-

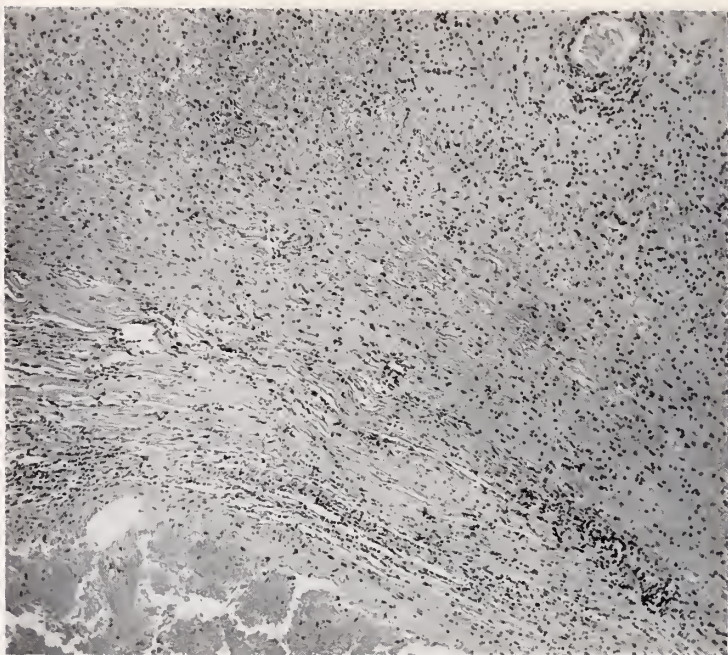


FIG. 2. The edge of the tuberculoma with its caseous center is shown at lower left. The vessel at upper right shows an inflammatory reaction involving the entire wall. (Hematoxylin and eosin stain; $\times 80$)

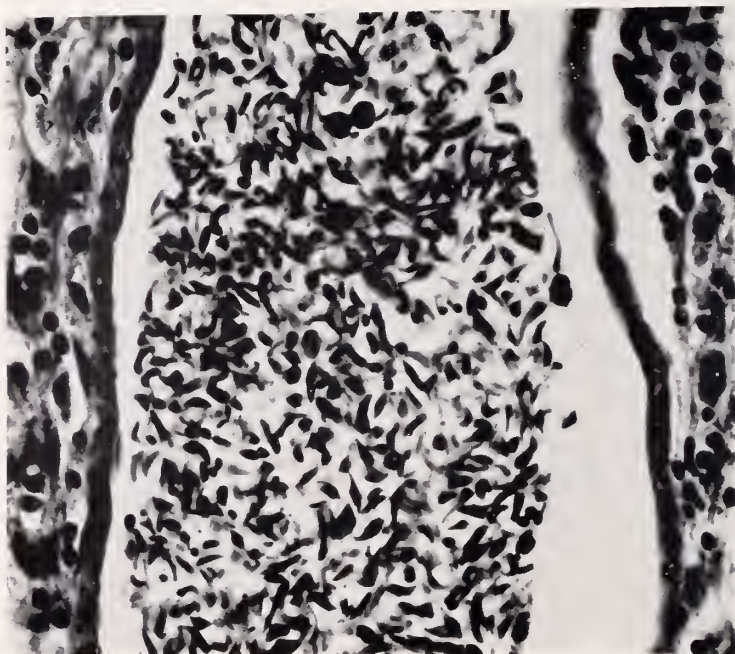


FIG. 3. Densely packed sickle cells fill a vessel in the vicinity of the tuberculoma. Note that almost no normally shaped red blood cells are present. (Hematoxylin and eosin stain; $\times 500$)

cytic infiltration and necrosis of all the vascular coats, particularly the adventitia (fig. 2). Marked thickening and fibrosis are evident in the leptomeninges, which are diffusely infiltrated with lymphocytes and epithelioid cells. Tubercles of small size are scattered throughout the subarachnoid space, and here the vessels show changes identical with those in the brain. A great many of the blood vessels are engorged with red blood cells; those closest to the tuberculous area show almost all of the red cells to be sickled and densely packed (fig. 3), whereas in other areas many of the red cells have a normal appearance. Ziehl-Neelsen preparations demonstrate many acid-fast bacilli throughout the exudative areas, but they are most conspicuous in the necrotic center of the large tubercle. With Herxheimer stains, fat deposits are noted in the lumen of an occasional small blood vessel, particularly in the subcortex. In the perivascular spaces about these channels there are many macrophages containing coarse granules which give the characteristic staining reaction for fat with Sudan IV. The cerebral tissue surrounding the embolized vessels shows no abnormality.

DISCUSSION

The difficulty of diagnosing other disease processes in the presence of sickle cell anemia is shown by the fact that in our case the cerebral symptoms were at first attributed to sickle cell anemia implicating the brain. Almost every type of vascular disorder of the brain has been encountered in sickle cell anemia. Scattered fat emboli, thrombosis (due to stasis and packing referable to the falciform erythrocytes), anemic infarction and softening, petechial hemorrhages, or combinations of these, are considered responsible for the neurological manifestations in this condition (3, 4, 5, 6). In our case, however, the neurologic symptoms were the result of a totally unrelated disease. In spite of the occasional fat embolus in the brain, the clinical manifestations in this patient could be readily accounted for by the dominant tuberculous disease that was present. Moreover, in the absence of cerebral changes in the regions supplied by the affected blood vessels, it is felt that the blood disorder did not play an important part in the significant cerebral symptoms, although it may have contributed to the rapid course of the final illness. A similar situation existed in the case reported by Vance and Fisher (7), in which the patient died of pulmonary fat embolism complicating sickle cell anemia. They also found fat emboli in the brain, but there were no clinical or pathological changes which could be ascribed to the presence of such embolization. Fat embolism occurring in sickle cell anemia is not uncommon and is attributed to necrosis of the marrow on the basis of severe circulatory disturbance in the bones (3, 6). Not all investigators, however, have been able to find fat emboli in the brain (4, 5) or in other organs (8). Furthermore, necrosis of the marrow was not present in our patient and the source of the emboli is a matter of conjecture.

Large concentrations of sickle cells were found only in those vessels close to the tuberculoma (fig. 3); in the rest of the brain only a relatively small proportion of the red cells were of abnormal shape. This is not uncommon when localized infectious processes occur in conjunction with sickle cell anemia. The high oxygen consumption of the bacteria and the reacting tissues, associated with vascular stasis, reduces the hemoglobin and the susceptible red cells become deformed. This mechanism has been used by Singer and Robin (9) as the basis of a diagnostic test for sickle cell anemia.

Tuberculosis is apparently no more common in patients with sickle cell anemia than in the negro population as a whole. Dolgopol and Stitt (10) found that 5.2 per cent of negro patients hospitalized for tuberculosis showed sickling, whereas the incidence in negroes in general is customarily given as 7.5 per cent (11). Only 2.5 to 10 per cent of people with "sicklemia" or "sickle cell trait" have the disease sickle cell anemia (11, 12).

A direct relationship undoubtedly existed between the patient's convulsions and some of the blood transfusions that she received. The first seizure followed by one day a transfusion given in October, 1946, and the second attack occurred two days after a transfusion in May, 1947. All succeeding convulsions came on in the hospital within 24 hours of a transfusion. Because of this apparent connection, the patient was given an intravenous infusion of 350 cc. of isotonic saline solution; 24 hours later she had a convulsion indistinguishable from the others.

One can only speculate as to the mechanism by which fluid administration caused the previously silent epileptogenic focus (the tuberculoma) to become active. It can be assumed that the tuberculoma in the right lateral fissure was the exciting agent here because of the aura of burning sensations in the left hand (which also occurred alone) and the fact that twitching of the left hand was the first convulsive movement in the Jacksonian march. Furthermore, the electroencephalographic finding of focal abnormality referable to the right parieto-occipital area strengthens the impression that the lesion was present at least 4 months before death.

Excessive water administration in relation to convulsions has been the subject of a great deal of investigation. Overhydration of the cerebral cells is postulated as predisposing to convulsions, the abnormal fluid intake resulting in blood dilution, hypochloremia and shift of water into the brain cells (13, 14, 15, 16, 17, 18, 19, 20). Toman and Goodman (21) showed that depletion of serum electrolytes lowered the threshold to electroshock convulsions to 44 per cent of normal four hours after intraperitoneal injection of isotonic glucose solution. The threshold returned spontaneously to 80 per cent of normal in 24 hours, but by giving hypertonic saline solution intravenously it reached 120 per cent after only 30 minutes. They also measured the intracellular fluid volume of cerebral tissue and produced only insignificant changes by lowering the serum electrolytes. There was a fairly good correlation, however, between the total serum electrolyte concentration and the seizure threshold, even though the amount of intracellular water was not appreciably altered. Stone (22, 23) found only minimal changes in the serum concentration and could not produce convulsions in epileptic patients by forcing fluids. The electroencephalogram in one epileptic was unaffected by giving 1000 cc. of normal saline intravenously (24). These investigations indicate that only *hypotonic* solutions caused convulsions, whereas normal or hypertonic fluids failed to produce them. In the case herein reported, only normal saline and blood were given, both presumably isotonic. For this reason, apparently neither overhydration of cerebral cells nor alterations of serum electrolytes can explain this patient's convulsions.

Increased intracranial pressure has been cited as another possible mechanism

for convulsions in susceptible individuals (19, 25), although Penfield and others (26) deny that they are brought on in this way. It is conceivable that in our case congestive heart failure (precipitated by increasing the blood volume with a heart diseased by severe chronic anemia) could have produced such a rise in intracranial pressure. At no time, however, did the patient show any evidence of either heart failure or increased intracranial pressure, and the fact that the convulsions did not characteristically come on until 24 to 48 hours after intravenous fluids is a further indication that the seizures did not occur on this basis.

Pagniez and Leroud (27) reported a patient with unsuspected cerebral metastases from a pulmonary carcinoma who had several Jacksonian attacks in the course of serum sickness with urticaria. The convulsions ceased with the disappearance of the allergic phenomena. There was probably sufficient cerebral edema to activate an otherwise silent epileptogenic focus. The occurrence in our patient of a convulsion following saline solution, however, eliminates allergic edema and red cell agglutination as responsible factors.

Transfusions in sickle cell anemia patients are not without hazard and several fatalities have been reported. Walker and Murphy (28) described the case of a boy of 12 with sickle cell anemia who had a convulsion 20 hours after a blood transfusion and died a few hours later of a massive cerebral hemorrhage. He had had twelve previous transfusions without incident, and there were no evident vascular abnormalities at autopsy. The authors felt that the site of the hemorrhage had previously undergone softening (due to anemia and circulatory stasis) and that the hemorrhage was a terminal event not related to the transfusion. They found support for their explanation of hemorrhage occurring in such a situation in the concept of Globus and Strauss (29), who showed that hemorrhage, even with normal blood vessels, could take place into an area of preexisting softening because the principal support of the blood vessels, that is, intact cerebral tissue, was thereby removed; changes in intravascular pressure could then result in massive hemorrhage.

The danger of transfusing *sickled* erythrocytes into patients with sickle cell anemia has been pointed out by Tomlinson (30) and others. This is particularly liable to occur in hospitals where blood from the patient's relatives (who frequently have sickle cell anemia themselves, the trait being inherited as a Mendelian dominant) is given to the patient after the usual compatibility tests. Tomlinson showed also that storage of blood and its withdrawal by vacuum methods increased the number of sickle cells in donors with sickle cell anemia. Singer and Robin (9), on the other hand, found that the survival time of sickled red cells transfused into patients with sickle cell anemia was normal (100 to 120 days). In any case, our patient, as nearly as we can determine, received no blood from her own relatives.

We have, then, no satisfactory explanation for the coincidence of the patient's convulsive seizures with the infusion of blood and saline. Convulsions as a reaction to transfusions are not uncommon and the tuberculoma, as a space-consuming lesion, could, in its own right, produce epileptiform attacks. It is not unlikely that there was some change in the cerebral tissue adjacent to the tuberculoma

and probably elsewhere in the brain as the result of the infused fluids, but, unfortunately, none of the commonly held theories concerning the relationship between convulsions and fluid administration provides a substantial clue as to the nature of such a change in this case.

SUMMARY AND CONCLUSIONS

1. A case of sickle cell anemia of many years' duration with a fatal termination is described. At autopsy, an intracranial tuberculoma with tuberculous meningitis was found. The clinical course was marked by convulsions which bore a definite time relationship to the infusion of blood or normal saline.

2. The pathological changes in sickle cell anemia affecting the brain are reviewed.

3. In a search for an explanation for the coincidence of fluid administration and the convulsive seizures, all of the currently accepted theories were considered, but found unsatisfactory.

We wish to express our sincere thanks to Dr. Joseph H. Globus, whose helpful advice and constant encouragement were indispensable in the preparation of this paper.

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COINCIDENTAL PSEUDOMUCINOUS CYSTADENOCARCINOMA OF THE OVARY AND ADENOCARCINOMA OF THE RECTOSIGMOID COLON

REPORT OF A CASE

HERMAN D. ZEIFER, M.D. AND MYRON E. STEINBERG, M.D.

From the Surgical service of Dr. John H. Garlock and the Gynecological service of Dr. Morris A. Goldberger

Since Billroth (1) reported the first case of multiple primary tumors in 1869, the literature has abounded in reports of this significant phenomenon which demonstrates that the presence of one malignancy does not preclude the development of another. On the contrary, it may well be that individuals who have or have had one cancer are more likely to be afflicted with a second malignancy than are normal persons liable to the development of their first.

Warren and Gates (11), in 1932, found the calculated incidence of multiple primary malignancy in cancer cases to be 3.9 per cent, a figure greater than that calculated on the basis of chance occurrence. The conclusion reached was that an individual with one cancer is more apt to develop a second than would be expected from the standpoint of chance alone. This would imply a predisposition or susceptibility to cancer in certain persons, or the action of some factor, present in these individuals, favoring the development of malignancy.

Bugher (2), in 1934, reported the results of a series of 4,394 necropsies; in 983, or 22.3 per cent of these, death was due to cancer, and in 30, or 3.1 per cent, there were multiple primary malignancies. He computed the expected occurrence of coincidental lesions from the mortality statistics of cases of cancer in the United States, and found that this figure was exceeded by the actual rate. The same conclusion was arrived at by Lombard and Warren (7) in 1943, and by Warren and Ehrenreich (12), who reviewed a larger series of cases in 1944, and found the incidence of multiple primary malignancy to be 6.8 per cent of all cancer cases.

In a review of the literature, we have been able to find only 12 reports in which the ovary and large bowel were each the seat of a primary carcinomatous growth.

In table I are listed the tumor types found in these cases.

CASE REPORT

History: Mrs. M. C., (Mount Sinai Hospital #583284), aged 34 years, was admitted to the Gynecologic Service on July 8, 1948 with the chief complaint of constipation of increasing severity and lower abdominal swelling. She had been well until March, 1948, at which time she first became aware of slowly increasing constipation. At the onset, she still had spontaneous bowel movements, but for a month prior to her admission to the hospital laxatives were necessary, and on one occasion, gross red blood was noted in her stool. Four months earlier, she noted increasing abdominal distention together with a decrease in the calibre of the stool. Her appetite was good; there was no loss of weight, nausea, vomiting, or pain. Three weeks before admission, several enemas were administered with

marked relief of the abdominal distention; following these, the patient discovered a mass in the lower abdomen never detected previously.

Her menses began at the age of 12 years, and occurred regularly once a month each of 3 to 4 days duration. Her last menstrual period occurred on July 2, 1948. She had a miscarriage at 3½ months, 8 years ago. Repair of a fistula-in-ano was performed in July, 1947. The family history revealed that the patient's father died of carcinoma of the rectum. Six siblings were living and well.

Examination: There was a mass in the lower abdomen which was soft, non-tender and cystic, and extended upward to the level of the umbilicus. The vulva and vagina were normal; the cervix was slightly irregular due to the presence of Nabothian cysts. The uterus was found to be displaced to the right by the mass felt per abdomen, which seemed to extend into the left broad ligament. There was a hard, nodular mass 3½ inches from the anal verge. It was fixed to the sacrum on the right and did not seem to be related to the suprapubic abdominal mass.

TABLE I

AGE	OVARIAN TUMOR	COLONIC TUMOR	AUTHOR
28	Adenocarcinoma	Colloid carcinoma, colon	Cimoroni (3)
32	Adenocarcinoma	Adenocarcinoma, rectum	Seelaus and Haskell (10)
40	Cylinder cell carcinoma	Carcinoma, sigmoid	Goullioud (4)
41	Papillary adenocarcinoma	Mucinous adenocarcinoma, rectum	Warren and Ehrenreich (12)
42	Epithelioma	Carcinoma, colon	Goullioud (4)
45	Adenocarcinoma	Adenocarcinoma, colon	Harbitz (5)
48	Papillary adenocarcinoma	Adenocarcinoma, cecum	Lemson (6)
53	Carcinoma	Carcinoma, cecum	Harbitz (5)
54	Papillary cystadenocarcinoma	Columnar carcinoma, colon	Young (13)
67	Adenocarcinoma	Adenocarcinoma, cecum	Warren and Ehrenreich (12)
—	Carcinoma	Carcinoma, rectum	Rau (8)
—	Papillary cystoma	Adenocarcinoma, colon	Schreiner and Wehr (9)

Sigmoidoscopy: The sigmoidoscope could not be passed beyond 12 cm., where there was evidence of bleeding and marked narrowing and angulation. The mucosa of the rectum appeared to be normal. It was, however, the impression of the examiner that there was organic stricture of the colon at the rectosigmoid junction. Nevertheless, one could not be sure that the obstruction was not due to extrinsic pressure from above by the pelvic tumor mass.

X-ray examination: Barium enema examination revealed a complete obstruction to the flow of the barium at the level of the rectosigmoid colon. The upper portion of the rectum was compressed by a large extrinsic pelvic mass. The mucosal pattern of the rectosigmoid appeared to be irregularly involved at its proximal extremity. From the findings in this roentgen examination, it was suggested that there was not only extrinsic pressure by the pelvic mass on the colon, but probably also infiltration of the colon with involvement of the mucosa. Intravenous pyelogram was reported as showing the upper urinary tract normal bilaterally. The urinary bladder was found to be depressed on the right by the pelvic mass. X-ray examination of the chest was negative.

Laboratory data: Hemoglobin 12.5 gm., white blood cells, 7,500, with 60 per cent segmented and 3 per cent non-segmented polymorphonuclear leukocytes; 31 per cent lymphocytes; 4 per cent monocytes; 1 per cent eosinophiles; and 1 per cent basophiles. The

erythrocyte sedimentation rate was 30 mm per hr. The Frei test was negative. The blood Wassermann test was negative. The blood urea nitrogen was 8 mg. per cent.

Course: The patient was prepared for operation with a low residue diet, daily colonic irrigations, and 4 gm. of sulfasuxidine 4 times a day for 8 days. Since it was felt that this patient had a cystic ovary on the left and possibly a carcinoma of the lower colon, the surgical consultant was requested to be present at the operation, should radical extirpation of the rectum and rectosigmoid be necessary.

Operation: Under ether-cyclopropane anesthesia, laparotomy was performed through a left paramedian incision (Dr. N. Mintz). A tense solid and cystic left ovarian mass, about 5 inches in diameter, was encountered. It was greenish-yellow, smooth in outline, and freely mobile. It was not adherent to the rectum or rectosigmoid. The right ovary was

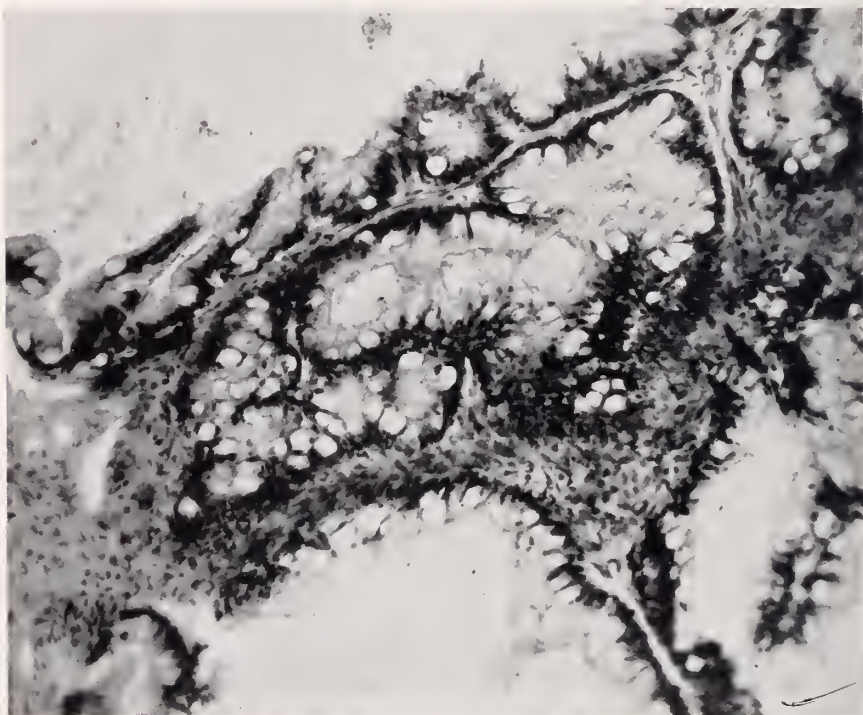


FIG. 1. Photomicrograph ($\times 200$) of pseudomucinous cystadenocarcinoma of ovary showing an area of tall, clear, columnar cells with small basal nuclei, characteristic of the pseudomucinous tumors of the ovary.

twice normal size but appeared grossly normal. The uterus appeared normal. Because of the presence of the left ovarian mass, visualization of the rectosigmoid was not possible at this time. On palpation, however, the rectosigmoid seemed to be the site of an intrinsic tumor mass. The liver was normal. Total hysterectomy and bilateral salpingo-oophorectomy were performed. Following this procedure, visual and palpatory examination of the left colon revealed the presence of a tumor involving the upper rectum and rectosigmoid at the level of the cul-de-sac peritoneal reflection. The tumor was about the size of a tangerine. The retroperitoneal tissues were somewhat edematous at the base of the rectosigmoid and sigmoid mesentery, and many enlarged, hard lymph nodes were palpated in the mesentery up to the origin of the inferior mesenteric artery. Abdominoperineal resection of the rectum and rectosigmoid was then performed, (Dr. S. H. Klein).

Surgical specimen: The ovarian tumor in the collapsed state measured 18 x 15 x 6 cm. Obvious ovarian tissue was not found grossly. The serosa was smooth, shiny, and even, save for one 3 mm., firm, white nodule which did not resemble the remainder of the tumor. The interior of the specimen was found to have an irregular, nodular wall plastered with thick, mucinous, yellow-green tumor masses, all of which were quite sticky, irregular, and soft. There were several small papillary growths on the interior of the wall in addition to the larger masses. On further examination the tumor was found to be multiloculated, divided by delicate translucent septa. The uterus was the size of a small orange. The myometrium was thin and even. The posterior muscle was irregularly thickened by whorled fibrous tissue suggesting adenomyosis. The cornua were intact. The cervix contained a few Nabothian cysts. It was free of erosions. The tube could be easily probed and the

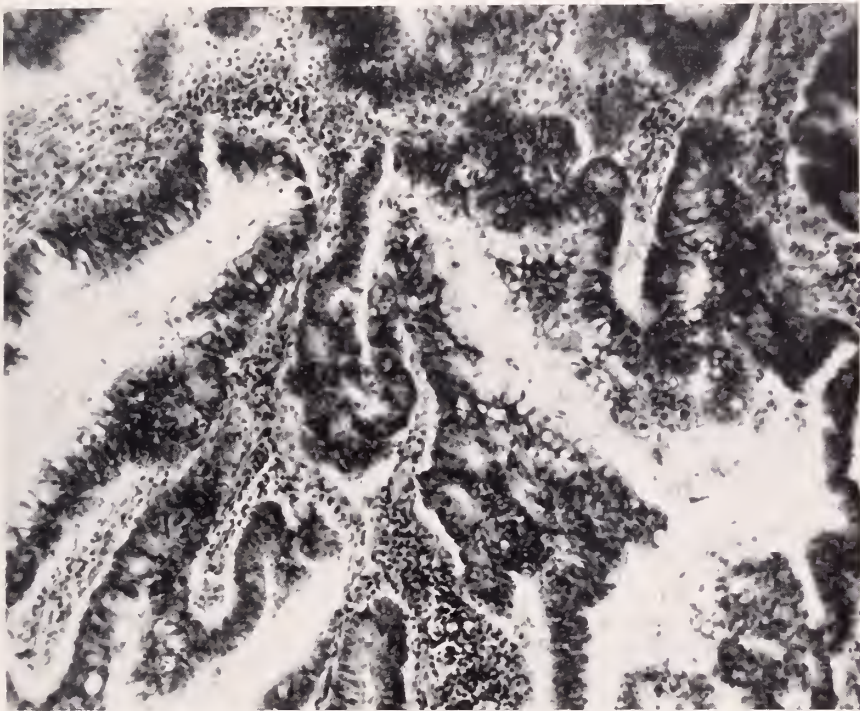


FIG. 2. Photomicrograph ($\times 200$) of section from the adenocarcinoma of the rectosigmoid demonstrating low columnar cells with deep staining cytoplasm and large irregular hyperchromatic nuclei.

fimbriae were delicate. The right ovary was the size of a walnut; its capsule was free of tumor. On section, the parenchyma appeared somewhat edematous. Several pea-sized, regressing corpora lutea were found.

The rectosigmoid tumor was part of a second specimen consisting of the rectum with perianal skin and 12 cm. of sigmoid colon. The rectum was pale with well preserved mucosa. Fifteen cm. above the anus at the rectosigmoid junction, was a raised cauliflower-like tumor, 5 cm. in diameter, with an irregular polypoid edge and ulcerated center. It was rather mucoid. The tumor completely encircles the lumen and there was slight dilatation of the proximal sigmoid. Several fleshy lymph nodes were found in the adventitia of the rectum. One of these was large and filled with pale sticky material. The tumor itself invaded the muscularis but did not appear to infiltrate the serosa.

Microscopic observations: The ovarian tumor presented histologic features of a pseudo-mucinous adenocarcinoma (fig. 1).

The right, normal ovary disclosed a hemorrhagic corpus luteum and cystic follicles.

The neoplasm of the colon revealed the structure of an adenocarcinoma (fig. 2). The lymph nodes were free of metastatic involvement.

Post-operative course: The immediate post-operative course was uneventful until the third day when nausea, vomiting, and abdominal distention occurred. X-ray examination and the clinical appearance of the patient suggested intestinal obstruction in the region of the jejunum. Because the colostomy functioned on the fourth post-operative day, the patient was treated conservatively with the Miller-Abbott tube, intravenous glucose and saline, and multiple whole blood transfusions. Rising temperature and pulse, however, and persistent abdominal distention in spite of the functioning colostomy indicated unrelieved obstruction. On the seventh post-operative day, laparotomy was performed. Obstruction of a loop of small intestine around the colostomy was relieved. The loop of small intestine proximal to the point of obstruction was found riddled with small tension ulcers, one of which was spontaneously leaking gas bubbles. Approximately one foot of small intestine proximal to the obstruction was resected and end to end anastomosis performed. The patient subsequently did well except for a wound infection which required incision and packing for drainage. Twenty days post-operatively, a small bowel fistula made its appearance at the upper angle of the wound which under conservative management closed down spontaneously.

COMMENT

The postulates laid down by Billroth (1) have largely been discarded since modern advances in diagnosis and therapy nullified his third dictum that each tumor must produce its own metastasis. We feel, however, that the case herein reported satisfies fully the criteria set forth by Warren and Gates (11), namely, that each tumor must present a different histologic picture of malignancy, each tumor must be grossly distinct, and that the probability of one metastasizing from the other must be excluded. With these points in mind, the specimens were studied by Dr. Alice Bernheim, assistant pathologist of the Mount Sinai Hospital, who felt that each tumor was independent and primary in its site of origin.

The relative youth of our patient, 34 years, as compared with the average age reported for all cases of multiple malignancy, 54 years (Warren and Gates 11), is a rather unusual feature.

Another point of interest is the fact that the presence of both lesions was considered preoperatively, and, with this in mind, the operative procedure was the combined undertaking of the Departments of Surgery and Gynecology.

SUMMARY

A case of coincidental primary carcinomata of the rectosigmoid colon and of the left ovary in a 34 year old woman is reported, and the pertinent literature is briefly reviewed.

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POLYMYXIN EFFECTIVE IN THE TREATMENT OF PYOCYANEUS SEPSIS; REPORT OF A CASE

ROBERT S. WALLERSTEIN*, M.D.

New York, N. Y.

In collaboration with

EMANUEL B. SCHOENBACH†, M.D.

Baltimore, Md.

Bacillus pyocyaneus septicemia was in the past generally resistant to treatment and usually had a fatal termination. The literature contains only twenty reports (1-20) recording a total of 28 cases in which the blood culture was positive and recovery eventuated. The advent of the chemotherapeutic agents and the antibiotics with antibacterial activity against Gram-negative organisms has thus far not materially enhanced the therapeutic results. A few recoveries have been attributed to the use of both sulfonamides (17, 19) and streptomycin (20) but the overall results have not been encouraging.

Reimann et al. (21) found that adequate dosage of streptomycin could control *pyocyaneus* infection only occasionally and then only when the bacteria were of susceptible strains. Stanley (22) in a comprehensive review on the subject of *bacillus pyocyaneus* infections concluded for both sulfonamides and streptomycin that "there is a large variation from strain to strain in sensitivity to both these substances and a fair proportion are initially resistant". Of the four cases of septicemia with this organism that he treated, all died. Robitzek and Prausnitz (23) likewise felt that sulfonamides and streptomycin both had limited effectiveness experimentally and clinically, and then only against susceptible strains. In experimental work employing mice, Jones et al. (24) did feel that they had demonstrated a fair degree of protection by streptomycin.

In 1947, three groups of workers (25, 26, 27) independently reported the isolation from sterile culture filtrates of a soil bacillus of a new antibiotic with a remarkable antibacterial specificity for the Gram-negative bacteria exclusively (26, 27, 29, 30). This again raised the hope that an agent was on hand that would be potent against those Gram-negative organisms which reacted only indifferently to the previously available antibacterial agents. This was named Polymyxin (D) by Stansly et al. (26) after its isolation from the *Bacillus Polymyxa*. Ainsworth et al. (27) isolated it from the closely related *Bacillus Aerosporus* and named it Aerosporin. Aerosporin has since been designated as Polymyxin B. Though the two are chemically dissimilar, (28) their spectra of bactericidal activity coincide.

Polymyxin was soon found to be effective against *bacillus pyocyaneus* *in vitro* (26, 29, 30, 31) and *in vivo* in mice (30). Furthermore strains resistant to polymyxin did not develop under conditions which readily yielded strains com-

* From the Second Medical Service of the Mount Sinai Hospital, New York, N. Y.

† The Department of Preventive Medicine, The Johns Hopkins University School of Medicine, Baltimore, Md.

pletely resistant to streptomycin (26, 27, 30). Because of the uniform activity of polymyxin against strains of bacillus pyocyaneus and the ineffectiveness of the other antibiotic agents in infections due to this organism, polymyxin was used in the following case of bacillus pyocyaneus septicemia. In this case the septicemia followed a protracted labor which ended with Cesarean section and was complicated by a renal shutdown. It is being reported to call attention to the undoubted clinical therapeutic efficacy of this agent in this very grave condition.

CASE REPORT

History (Mt. Sinai Hosp. adm. #587105). The patient, a woman aged 36 years, entered another hospital in labor. The pregnancy had been uneventful. Her blood pressure averaged 115 systolic and 70 diastolic and the urine was negative for albumin throughout the pregnancy. Labor was difficult and at the end of seven hours the blood pressure had risen from an initial 114 systolic, 68 diastolic to 190 systolic, 110 diastolic and the urine at that time showed a four plus albumin. She was therefore subjected to an extra-peritoneal Cesarean section under spinal anesthesia. The operation lasted three and a quarter hours. As a result of technical difficulties a large rent was made in the bladder and suprapubic cystostomy had to be performed. A living child was delivered. The patient received a 1,000 cc. of whole blood during the operation.

During the subsequent eight days the patient was oliguric and became increasingly uremic. On the first post-operative day the NPN was 62 mg. %, the creatinine 5.4 mg. %, the CO₂ 54 volumes %, the chloride 600 mg. %, the sugar 109 mg. %, and the hemoglobin 55 %. In the course of the eight days the azotemia increased so that on the last day of her stay in that hospital the NPN was 174 mg. %, the uric acid 11.6 mg. %, the creatinine 12 mg. %, the CO₂ 38 volumes %. The daily urinary output had gradually fallen from 850 cc. to 45 cc.; there was never complete anuria.

The fluid intake had been kept up to levels of about 2000 cc. daily with 300 to 500 cc. of sixth molar lactate intravenously to combat acidosis. Her blood pressure had varied from 90 systolic and 60 diastolic to 170 systolic and 90 diastolic. On the fifth and seventh post-operative days she received 500 cc. whole blood transfusions. Her temperature was 102 °F. on the first post-operative day but then returned to normal until the morning of transfer to the Mount Sinai Hospital. On that morning she had three shaking chills, her temperature rose to 102°F. and she vomited repeatedly. She was transferred to the Mount Sinai Hospital for evaluation as to the therapeutic indications for use of the "artificial kidney".

Examination on admission to the Mount Sinai Hospital. The patient appeared to be acutely ill but alert and well-oriented. Her temperature was 104°F., her pulse 120 and her blood pressure 160 systolic and 60 diastolic. The fundi were normal. The breath was not uremic. The posterior pharyngeal wall showed some clotted blood. There was no glandular adenopathy. The lungs showed a massive right pleural effusion with flatness and diminished to absent breath sounds. There were coarse rales at both bases. The heart showed a diastolic gallop over the sternum and aortic area with a systolic murmur at all valvular areas. The abdomen was distended. The liver was five fingers and the spleen two fingers below the costal margin. There was a suprapubic wound with the tube removed and the wound taped together. An indwelling catheter was in the urethra. There was a two plus ankle and pre-sacral edema. All peripheral pulses were palpable.

Laboratory data: The hemoglobin was 9 Gm.; the red blood count, 2,900,000; the white blood count, 20,800 with 80% polymorphonuclears, 10% non-segmented forms, and 10% lymphocytes. There was slight toxic granulation. The urine showed a pH of 5.5, one plus albumin, no sugar or acetone, a specific gravity of 1.012 and a very white high blood cell content many of these being in clumps. The sedimentation rate (Westergren) was 20 mms/hr. The venous pressure was 14.5 cm. with a rise to 19 cm. on right upper quadrant pressure. The circulation time with calcium gluconate was 10 seconds. Blood chemical determina-

tions on admission showed a urea of 123 mg. %, creatinine 19.7 mg. %, uric acid 11.6 mg. %, NPN 175 mg. %, chlorides 562 mg. %, CO_2 40 volumes %, total proteins 5.4 Gm., phosphorus 6.3 mg. %, and calcium 9.3 mg. %. The blood Wassermann test was negative. The electrocardiogram was normal.

Course: The patient was manifesting evidence of a partial renal shutdown probably due to a combination of pre-renal azotemia (operation, shock, strain of labor), renal tubular damage of the lower nephron type (post-partum with sepsis), and post-renal azotemia (inflammatory swelling around the ureters due to operative manipulation and infection). Because of the renal shutdown and the taxing of the circulation with intravenous fluids, congestive heart failure had been precipitated. There were gallop rhythm, rales at both lung bases, right pleural effusion, ankle and sacral edema, and an engorged liver. The rapid circulation time in the presence of heart failure was attributed to the concomitant anemia. The high fever was felt to be related to the wound and urinary tract infection.

The patient was placed on Crystieillin 300,000 units daily and streptomycin 0.5 Gm.

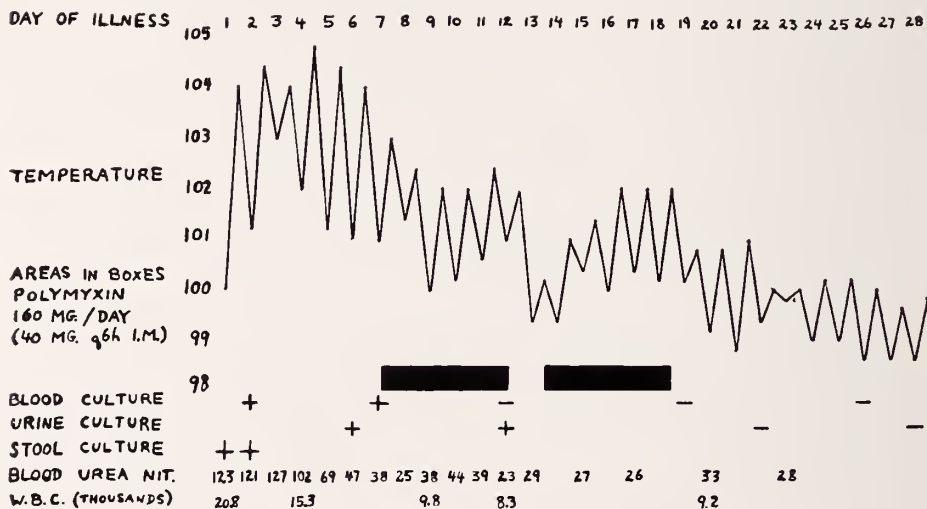


FIG. 1. CHART OF DATA DURING FIRST FOUR WEEKS

Patient A. C., *Bacillus pyocyaneus* septicemia, female, age 36.

every six hours to combat the urinary tract infection. She was subjected for a preliminary period to conservative management for evaluation of her suitability for the "artificial kidney". She was given no fluids parenterally and only up to 800 cc. of orange juice by mouth each day. The urine flow through the indwelling catheter was measured. The patient did extremely well on this restricted regimen. Spontaneous diuresis started soon after admission. Further overloading of the circulation was prevented.

The urinary output the first day was 3,320 cc. and for the next three days was 5,300 cc., 5,870 cc., and 4,130 cc. With this diuresis the signs and symptoms of congestive failure began to recede. As water and salt were lost through the urine an increasing fluid intake was permitted. On the third day fluids were allowed ad lib and meals consisting of rice, butter, and sugar were given. On the fifth day the patient was placed on the regular hospital soft diet. Blood chemical determinations rapidly reverted towards normal with the successive daily urea levels being (in mg. %) 123, 121, 127, 102, 69, 47, 38, and 25 at the end of the first week. The creatinine similarly fell from 19.7 mg. % to 1.8 mg. % during the same period.

However, despite penicillin and streptomycin therapy, the temperature remained elevated at the same high levels as on admission, spiking daily to 104°F. A blood culture taken

on admission was positive for bacillus pyocyaneus. The same organism was also recovered from urine and stool cultures. The organism was resistant *in vitro* to 100 units of streptomycin per cc., that is, more than 500 times as resistant as the standard organism; resistant to 50 units of penicillin per cc., that is, more than 2500 times as resistant as the standard organism; and resistant to 100 mg. % of sulfadiazine. In view of the high *in vitro* resistance and the lack of clinical response, both penicillin and streptomycin were stopped on the fifth hospital day. At that time the temperature was 104°F., the white blood count was 15,250 and the hemoglobin 8.7 Gm.

Because of the known grave prognosis in this form of sepsis, the lack of response to the more readily available antibiotics (both *in vivo* and *in vitro*), and the reported sensitivity of bacillus pyocyaneus to polymyxin, a clinical trial with this agent was believed indicated. Polymyxin is a known nephrotoxic drug and on the day of institution of polymyxin therapy, recovery from the cardiorenal damage was far from complete. The blood urea was still 38 mg. % and the creatinine 2.2 mg. %. However it was felt that the desperate clinical situation justified the risk involved in administering this drug.

Accordingly polymyxin B therapy was started on the seventh hospital day with a dosage schedule of 40 mg. intramuscularly every six hours. Sensitivity studies revealed that the strain isolated from the patient's blood was susceptible to less than 0.1 mcg of polymyxin B per cc. The renal status was closely observed. The blood urea fluctuated between 25 mg. % and 44 mg. % throughout the course of therapy. The urine which had not been negative since admission continued to show a two plus albumin and many white blood cells and red blood cells. However, it was noted at this time that vesico-vaginal fistula was present, evidently due to the previous operative intervention. Methylene blue placed in the bladder through a catheter appeared from a fistula situated just above a sloughing upper cervical lip.

The temperature response to the polymyxin was slow but steady (see figure 1). After five days of therapy, when a total of 800 mg. had been administered, the temperature range had come down to between 101°F. and 102°F. Blood and urine cultures promptly became and remained sterile. After five days, therapy was discontinued for a day while a fresh supply of polymyxin was obtained. During that day the temperature ranged between 99°F. and 100°F. Another 800 mg. of polymyxin B were then obtained and during the five days of administration of this supply, the temperature again rose to between 101°F. and 102°F. It fell to normal upon cessation of therapy and remained normal thereafter. Blood and urine cultures have been persistently negative. Patient is now clinically well, free of signs of sepsis, and with a normal cardiorenal system. Her sole remaining disability is the vesico-vaginal fistula, for which she is awaiting surgical repair.

DISCUSSION

It may be assumed that the use of polymyxin B or "aerosporin" played a determinant role in the favorable course of events in this case. Though spontaneous recoveries from pyocyaneus sepsis are known, they are rare and they run a long and stormy course. In our case the clinical course was marked by steady deterioration up to the time specific therapy with this agent was initiated. Additional cases of severe pyocyaneus sepsis observed by one of us (E. B. S.), likewise responded to polymyxin therapy. Their ages varied from 8 months to 60 years. Some had positive blood cultures. The majority had not responded to penicillin, streptomycin, and sulfonamides. The organisms were resistant *in vitro* to over 250 mcg. of streptomycin and penicillin. Sensitivity to polymyxin varied between 0.5 and 2.5 mcg. Negative blood cultures were obtained within 24 hours after the onset of therapy, with even burned infected areas becoming sterile (33, 34).

Likewise in our patient extreme resistance of the infecting organism was demonstrated *in vivo* when tested with streptomycin, penicillin, and sulfadiazine. A trial of combined streptomycin and penicillin therapy before the nature of the bacteremia was known, had had no effect on the clinical course. Sensitivity of the organism to polymyxin was demonstrated *in vitro*. The clinical response can be evaluated from this report and the accompanying chart.

The possibility of drug fever due to polymyxin B is of interest. During the first five day course of the drug, the temperature fluctuated in the range between 101°F. and 102°F. A one day interruption in therapy ensued while a fresh supply was being obtained. During this day the temperature fell below 100°F. Upon reinstitution of therapy for five additional days the temperature again rose to febrile levels between 101°F. and 102°F. It promptly fell again after cessation of therapy and remained normal thereafter. Drug fever has not been noted with polymyxin D but it has been encountered with polymyxin B (aerosporin). This may well be another example.

Another point of significance is the use of this drug in the face of still unresolved and very severe recent acute renal damage. Polymyxin has been withheld from widespread distribution largely because of renal toxicity (30, 32). Yet, under properly controlled hospital conditions with a daily measure of the urinary output, blood urea nitrogen, and urinary albumin, it was possible to administer the agent without apparent aggravation of the already existing renal damage. In selected cases and in controlled settings it may be singularly the drug of choice and cause a reversal in the prognosis of what has up to now been a disease of almost uniformly fatal import.

SUMMARY

A case of bacillus pyocyaneus septicemia secondary to prolonged labor with Cesarean section complicated by renal shutdown is described. The organism showed extreme resistance towards streptomycin, penicillin, and sulfadiazine both clinically and *in vitro*. The employment of the new antibiotic, polymyxin B (aerosporin) resulted in prompt recovery. The sensitivity of the organism to polymyxin was demonstrated *in vitro*. The possibility of drug fever as a toxic effect is considered. The successful use of the drug, a known nephrotoxic agent, in the presence of acute renal damage is described. The risk was felt justified in view of the serious prognosis of the disease in the absence of treatment. The literature is reviewed disclosing a paucity of recovered cases, either spontaneous or due to the previously employed antibiotic agents, sulfonamides or streptomycin.

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OBSTRUCTION OF THE COMMON BILE DUCT CAUSED BY AN ERODING GALLSTONE

REPORT OF TWO CASES¹

DAVID ORRINGER, M.D.

Obstruction of the common bile duct as a result of erosion into it of a stone from the gallbladder is apparently a rare complication of cholelithiasis. A search of the literature of the past ten years and of the records of The Mount Sinai Hospital failed to disclose a single example. Rehfuess and Nelson (1) observed jaundice in some cases where a cystic duct stone protruded into the common duct and also as a result of compression of the common duct by a large stone in a diverticulum of the gallbladder. The latter may well represent the initial stage of the process by which a gallstone erodes into the common duct, thereby producing a fistulous communication. Bockus (2), in a discussion of spontaneous internal biliary fistulas, reviewed Naunyn's large series. Of a total of 178 cases, only 8 were limited to the biliary tract.

The two cases of obstruction of the common duct due to eroding gallstones to be reported herein occurred in elderly men, both of whom had jaundice as the predominant symptom. In the first, pain preceded the jaundice, while in the second, pain was entirely absent. At operation in both cases, a single, large, mulberry stone was found to have eroded through the wall of the gallbladder into the common bile duct.

CASE REPORTS

Case 1. History (Adm. #585629). J. C., aged 73 years, was admitted to The Mount Sinai Hospital September 17, 1948, with a history of upper abdominal pain of 2 weeks' duration. Mild at first, it increased in severity two days after onset and radiated to the back. Nausea accompanied the onset of the pain. Soon after, the urine became darker in color and the stools light-colored and loose in consistency. Jaundice appeared and increased progressively.

During the past 7 years, the patient had had 3 similar attacks of abdominal pain; there was no jaundice, however.

Examination. The patient appeared chronically ill and intensely jaundiced. The lungs were clear. The heart sounds were normal and no murmurs were heard. The blood pressure was 160 systolic and 80 diastolic. The liver edge was felt 2 fingerbreadths below the costal margin. There was slight tenderness in the right upper quadrant of the abdomen.

Laboratory data. Blood: hemoglobin, 13 Gm.; red blood cells, 4,290,000; white blood cells, 7,050, with a normal differential; sedimentation rate, 74 mm. in 1 hour. Urine: bile, 3 plus; urobilin, 1:5. Blood urea nitrogen, 16 mg. per cent; blood sugar, 103 mg. per cent; cholesterol, 195 mg. per cent; total protein, 7.6 Gm.; bilirubin, 9.6 mg. per cent; Van den Bergh, direct prompt positive; formol gel, positive; cephalin flocculation, 4 plus; thymol turbidity, 4 plus; alkaline phosphatase, 24 King-Armstrong units; prothrombin time, 19.5 sec. (control, 12 sec.). The stool was light tan in color and contained no stercobilin. Duo-

¹ From the Surgical Service of Dr. Arthur S. W. Touroff, The Mount Sinai Hospital, New York.

denal drainage studies indicated complete biliary obstruction with normal pancreatic secretion. An electrocardiogram showed no abnormalities.

Course. On Vitamin K therapy the prothrombin time became normal, and on the third hospital day the abdomen was explored. The gallbladder was shrunken and fibrotic. The common duct was dilated. A single mulberry stone, 2 cm. in diameter, was found impacted in the ampulla of the gall-bladder. It protruded through a fistula into the common bile duct. A cholecystectomy was performed. The fistulous opening in the bile duct was closed and a T-tube inserted. The postoperative course was uneventful. Urinalysis, 9 days after the operation, showed 3 plus bile and urobilin present in a dilution of 1:20. Thereafter the concentration of bile in the urine dropped rapidly, while the urobilin concentration rose to a peak, 1:400. At the same time, the jaundice diminished gradually.

A cholangiogram performed on the 16th postoperative day showed prompt entrance of the iodized oil into the duodenum. There was no evidence of obstruction. The T-tube was removed the following day, and the patient was discharged October 7, 1948, 18 days after operation.

The pathological diagnosis was "acute and chronic cholecystitis and cholelithiasis."

Case 2. History (Adm. #566394). B. G., aged 70 years, was admitted to The Mount Sinai Hospital June 20, 1947, complaining of clay-colored stools and dark urine for the past 2 weeks. Diarrhea, anorexia, and nausea were present during the same period. No fever or chills were noted. In the past 5 months, there had been a loss of 25 pounds in weight. Five days before admission, a physician observed that the patient was jaundiced.

Examination. The patient appeared well developed and well nourished, and not acutely ill. The skin and sclerae were jaundiced. The lungs were hyperresonant, and no rales were heard. There were no cardiac murmurs or thrills. The blood pressure was 170 systolic and 70 diastolic. The heart action was grossly irregular. The radial arteries were sclerotic. The liver was hard, with its edge 3 fingerbreadths below the costal margin. There was no abdominal tenderness or muscle spasm.

Laboratory data. Blood: hemoglobin, 14.6 Gm.; white blood cells, 6550, with 79 per cent polymorphonuclear leucocytes. Urine: there was an occasional trace of bile and urobilin in dilutions of 1:5 and 1:10. Sedimentation rate was 20 mm. in 1 hour. Blood urea nitrogen, 11 mg. per cent; cholesterol, 191 mg. per cent; cholesterol esters, 100 mg. per cent; thymol turbidity, negative; alkaline phosphatase, 33 King-Armstrong units; total protein, 6.2 Gm.; icterus index, 24; bilirubin, 4.2 mg. per cent; Van den Bergh, prompt positive; Kahn and Wassermann reactions, negative; cephalin flocculation, 1 plus.

X-rays of the abdomen revealed a large, elliptical, laminated opacity in the right upper quadrant, thought to be a gallstone.

An electrocardiogram showed auricular fibrillation with a very slow ventricular rate.

Course. The patient was prepared for operation with vitamin K, and on the 13th hospital day an abdominal exploration was performed. The colon, stomach and omentum were found adherent to the fundus of the gallbladder. When these organs were dissected free, the gallbladder was found to be connected by dense adhesions to the common bile duct. Further dissection revealed a wide communication between the gallbladder and the common duct. A partial cholecystectomy was performed, with removal of a huge gallstone, which occupied the lumen of the gallbladder and protruded into the common duct. No other stones were found. A T-tube was placed in the common duct and a large tube in the remnant of the gallbladder.

The patient's postoperative course was smooth. Biliary drainage, which at first was profuse, gradually diminished. Nine days after operation, urinary bile had decreased to 2 plus and urobilin was present in dilutions of 1:20. Thereafter, the urine became bile-free, and urobilin was present in normal concentration. The jaundice gradually subsided. The cholecystostomy tube was removed 12 days post-operatively.

Three weeks following the operation, alkaline phosphatase was 13.5 King-Armstrong units; icterus index was 12; bilirubin, 0.2 mg. per cent; and Van den Bergh, negative.

Cholangiography, on the day prior to discharge, showed prompt passage of the iodized oil into the duodenum. There was no evidence of obstruction. The T-tube was clamped off following this procedure and the patient discharged the next day, 33 days after operation.

The pathological report was "fragment of gallbladder showing acute and chronic non-specific inflammation with foreign body giant cell reaction and cholesterol crystals."

Three months after discharge, patient was seen in the Surgical Follow-Up Clinic. He looked and felt well and stated that his stools were of normal color.

COMMENT

Rehfuß and Nelson (1) suggest that when there are stones at the neck of the gallbladder or the beginning of the cystic duct, jaundice may occur as a result of one of three possible factors: 1. Protrusion of a cystic duct stone into the common duct, 2. Compression of the common duct by a large stone in a diverticulum of the gallbladder or, 3. Extension of spasm or inflammation from the cystic duct into the common bile duct. Thus, a single large stone impacted in the ampulla or fundus will usually produce jaundice and pain before erosion takes place. However, it seems possible that an impacted stone may erode through the gallbladder into the common duct over a long period of time without producing symptoms. When protrusion into the common duct ultimately occurs and results in biliary obstruction, symptoms may become manifest for the first time. The associated occurrence of an acute inflammatory reaction can hasten this process considerably. It is suggested that this was the mechanism of biliary obstruction in the two cases reported.

SUMMARY

Two cases of obstruction of the common bile duct, resulting from erosion of large stones from the gallbladder into the common bile duct, are presented. Both occurred in elderly men in whom there were minimal local physical findings immediately prior to operation.

I am indebted to Dr. Ralph Colp for permission to report Case 2.

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SCOLIOSIS—A CONCEPT OF ITS PATHOGENESIS

PRELIMINARY REPORT*

ALVIN M. ARKIN, M.D.

It has been suggested (1) that the structural changes in scoliosis can result from the arrest and distortion of epiphyseal growth by pressure. This asymmetrical pressure is produced by gravity acting upon the erect spine, once a functional curve has been initiated. The mechanism of production of functional curves remains to be considered.

The elasticity of the intervertebral discs, confined as they are under pressure by their surrounding structures, tends to resist lateral deviation of the spine. An asymmetrical force (and only an asymmetrical force) can produce a lateral curvature—by deformation (wedging) of these discs, producing a functional (reversible) curve. Symmetrical forces, of course, do not deviate the spine to either side.

On the other hand, a structural (irreversible) curve is produced by wedging of vertebral bodies. This is not due to bony compression, since normal bone when subjected to pressure does not collapse but rather hypertrophies. It can be due only to epiphyseal growth arrest or retardation. The growth arrest, in turn, is probably due only to the pressure mechanism previously described, as evidenced by the fact that the pattern of growth arrest follows, *pari passu*, the pattern of pressure distribution, even to the point of resumption of growth when the pressure is removed by recumbency (Cobb¹ found that "idiopathic" scoliosis stopped progressing when the patients were put to bed).

Cobb's observation indicates that in idiopathic scoliosis the initiating asymmetrical force does not contribute appreciably to the force of gravity in producing pressure arrest of growth, since removal of gravity alone, by recumbency, stops progression. In most cases of this type the initiating asymmetry is merely an habitual postural defect, which is important only because the curvature it produces causes asymmetrical distribution of gravitational stresses in the vertebral column, with resultant asymmetrical pressure-induced growth retardation. Such asymmetries are usually so minor in degree that they do not have enough force to deviate the spine against the elasticity of the discs alone, unless aided by gravity. Hence, in the functional stage, before structural changes have supervened, such curvatures disappear in recumbency.

In contrast with this type of asymmetry is the major asymmetry occurring, for example, after thoracoplasty. Here the curvature develops and progresses even in recumbency (2). Hence such major asymmetrical forces must certainly contribute appreciably to the force of gravity in producing pressure arrest of growth and wedging.

* From the Orthopedic Service of The Mount Sinai Hospital (Dr. Robert K. Lippmann), New York.

¹ Personal communication.

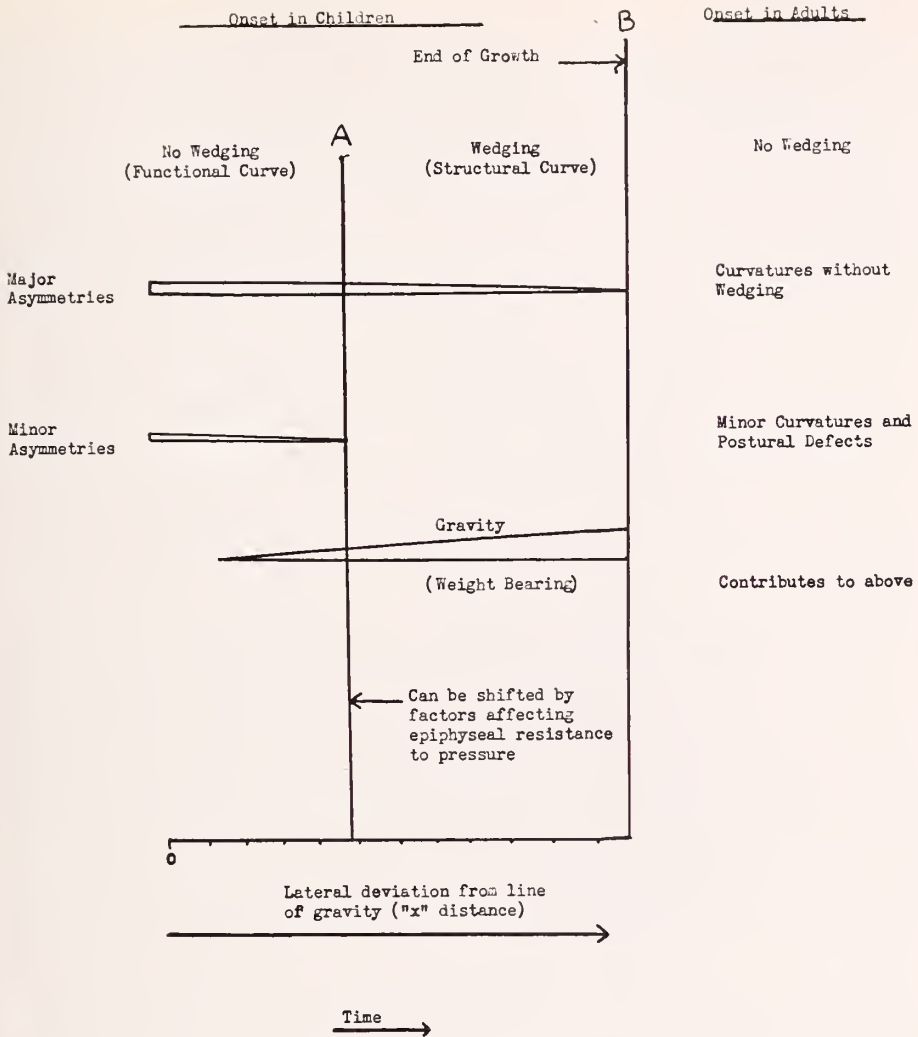


Diagram of pathogenesis of scoliosis

The line B divides the diagram into two parts. That part to the right of this line indicates curvatures beginning after growth has ceased. Wedging does not occur in these curvatures. The part to the left of line B diagrams the pathogenesis of scoliosis which begins in childhood. The initiating factors in the production of curvatures are listed at the far left. A major asymmetry, for example, may begin to act upon a straight spine. In time, and with increase in curvature, the contribution of the major asymmetry diminishes, denoted by the diminishing thickness of the adjacent horizontal line. As soon as the spine has started to curve, gravity begins its ever-increasing contribution to progression. The thickness of each line is intended to represent its contribution to the pressure falling upon the epiphyseal plate (gravity acting only in the erect position). The line A represents the degree of lateral deviation at which the combined pressures upon the epiphyseal plate become sufficient to cause appreciable asymmetrical growth arrest and hence marks the division between functional and structural curvatures. Factors which diminish the resistance of the epiphyseal plate to pressure, would have the effect of shifting the line to the left, and hence would facilitate the initiation and progression of wedging with only minor deviations from the vertical. The diagram is not intended to be quantitative in its relationships. It is intended to diagrammatically illustrate the main points of the concept proposed in this paper.

It is interesting to note that the spines of quadrupeds, being horizontal, are protected from gravity-induced stresses and hence "idiopathic" scoliosis does not occur. For example, circus horses habitually run around a ring in one direction, sometimes starting quite young, still never develop a scoliosis.² On the other hand, I am told that horses who from an early age pull a millstone around a circular mill develop a structural curvature of the spine which is permanent and easily recognizable, so that it is even possible to tell whether they habitually went to the right or the left. Obviously the compression of the spine into the collar substituted effectively for gravitational stress in converting an habitual curve into a structural scoliosis.

Here, then, is the cause of functional curvatures—asymmetrical forces. They can be divided into two groups, *major* or *minor*, depending upon whether they contribute significantly to gravity in the production of structural changes, once the functional curve is established.

Structural changes in functional curves are probably always caused by pressure arrest and distortion of growth. The pressure is due to gravity alone in minor asymmetries; to gravity plus a soft tissue "bowstring" effect in major asymmetries.

All other factors of etiological significance would appear to act in only one way, that is, to vary the resistance of the epiphyseal plate to pressure and, hence, to modify the susceptibility of the spine to structural changes. These changes will have to be superimposed upon a preceding functional curve, and these, of course, are extremely common. (Even if the functional curve operates for only part of a day—e.g., in school—it may, perhaps, still be effective in facilitating pressure arrest of growth, especially where the epiphyseal plate is unduly susceptible to pressure.) Factors such as rickets, heredity and sex fall into this group.

This concept of pathogenesis of scoliosis is summarized in the accompanying chart.

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² Dr. Henderson (veterinarian to Ringling Bros., and Barnum and Bailey): personal communication.

A BLEB TECHNIC OF ARTERIAL PUNCTURE

SAMUEL J. MEGIBOW, M.D., AND LESTER BLUM, M.D.

After many years of laboratory usage, arterial puncture has become a clinical commonplace. Its present application is largely limited to the withdrawal of specimens from peripheral vessels and arterial injection (1, 2). With the development of arteriography (3) and arterial infusion (4, 5, 6), the procedure will necessarily take on new technical aspects. Increasing experience has demonstrated its safety and freedom from complications.

When an artery is punctured, some leakage of blood following withdrawal of the needle is to be expected. This invariably takes place and serves as the basis of the mechanism that seals the leak. The peripheral arteries are either enclosed by sheaths derived from the deep fasciae or enveloped by a firm adventitia which is present as an ensheathing membrane down to the smallest visible branches. As the blood escapes through the needle tract, it forms a hematoma which collects within the adventitia or under the fascial sheath about the artery. As the tension increases, this encapsulated clot serves as a tampon shutting off the further escape of blood.

The normal clotting mechanism aids in two ways. It serves to thicken the adventitial hematoma and so make it a more effective plug; it also slows the movement of blood through the tract in the vessel wall.

There are certain circumstances in which this usual mechanism does not function. The visceral arteries are thin-walled despite their direct derivation from the aorta and have only thin peritoneum in apposition to them. When they are needled, it is common to have prolonged spurting from the site of puncture. When peripheral arteries are denuded of their sheaths, the same thing occurs. When an animal is heparinised, arterial puncture becomes fraught with danger regardless of the caliber of the needle. It is common in our experience to witness a spurting of blood from the site of an apparently closed puncture shortly after the administration of heparin. During the course of experiments involving heparinised animals, this persistent leakage from sites of arterial puncture developed into a major complication. Expediency demanded the development of a simple technic which is applicable to arterial puncture anywhere.

At the intended puncture site, an adventitial bleb of saline solution or gelatin, or blood is raised by inserting the tip of a 27 gauge needle into the outer tissue of the vessel wall. The arterial needle is then introduced through the bleb into the lumen of the vessel. When it is withdrawn, the blood seeping out tends to blow up the previously prepared bleb by infiltration and so produces a larger, more tenacious tampon. The production of the bleb prior to puncture accomplishes the following: it creates a thicker adventitia; it allows the formation of a more horizontal needle tract, so that a sealing valve action occurs (fig. 1).

Where the animal was heavily heparinised, this technic was only partially successful. Two further expedients were employed.

Iced saline was applied to a gelatin bleb to increase its viscosity and better

mechanically stem the escape of blood. The other adjuvant was the solution of protamine in the gelatine with the idea of having a local antagonistic effect to the heparin at the needle tract. There was no evidence of any benefit from the local use of protamine in this manner. Solutions of thrombin were not tried.

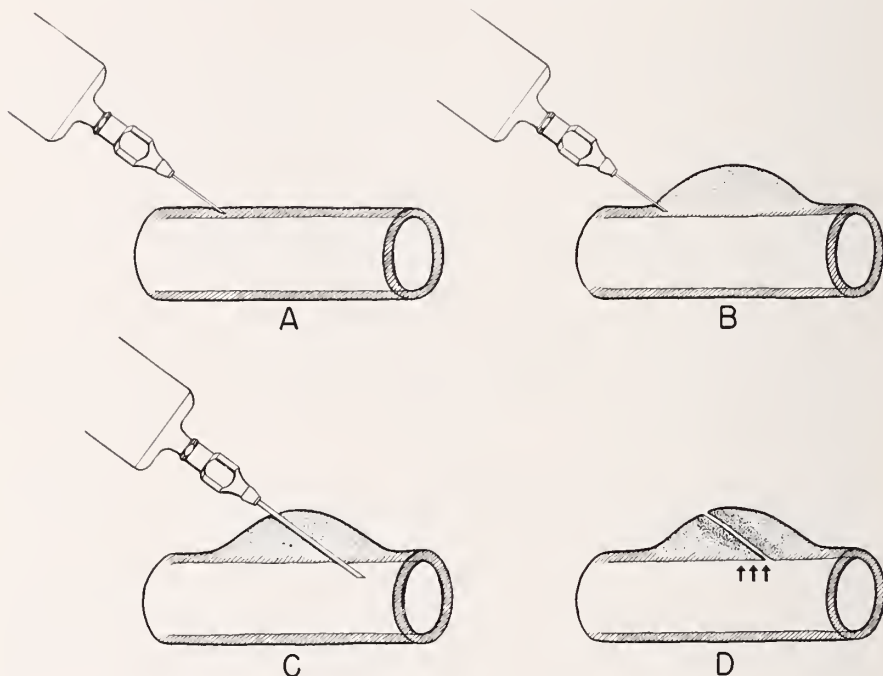


FIG. 1

SUMMARY

A method of preventing or minimising the escape of blood from the site of an arterial puncture is described. It consists of raising a preliminary bleb of fluid in the outer coat of the vessel, through which the arterial puncture is made. The effect is that of adding an extra adventitia and furthermore producing a sealing valve-like mechanism.

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ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

The Significance of the Gastric Acidity in the Surgical Therapy of Peptic Ulcer. A. WINKELSTEIN. Surg. Clin. North America, New York No., p. 255, April, 1947.

While peptic ulcer is probably a psychosomatic disease, the immediate mechanism of its production is the acid-pepsin factor. The author summarizes briefly his studies on the acid factor during the past 25 years. These studies reveal the following. (1) Gastric ulcer acidity is usually normal or low due to gastritis and duodenal inhibition. (2) Duodenal ulcer acidity is high due to vagus nerve influences and lessened duodenal inhibition. (3) Partial resection for "angle" gastric ulcer results in achlorhydria without recurrences. (4) Partial resection for duodenal ulcer leads to achlorhydria only in 55 per cent. Recurrences in those with post-operative free acidity are frequent (9 per cent). (5) Since this persistent free acidity is vagal, bilateral complete subphrenic vagotomy is advocated in addition to the partial resection (and also with gastroenterostomy). (6) Supradiaphragmatic vagotomy alone is viewed with some disfavor. (7) Vagotomy seems valuable for recurrent jejunal ulcers. (8) Recent studies confirm the previous finding that the night secretion is increased in duodenal ulcer. It is best controlled by intragastric drip therapy or vagotomy.

The Postgastrectomy Syndrome. D. ADLERSBERG AND E. HAMMERSCHLAG. Surgery, 21: 720, May, 1947.

A group of 14 patients, who for many years after partial gastrectomy for ulcer had been unable to gain weight and presented difficult nutritional problems, have been investigated. The symptoms were analyzed and divided into 2 groups: early and late postprandial symptoms. The early symptoms were caused by mechanical factors, small stomach and rapid emptying, and overflowing of the small intestine. The late symptoms were due to chemical factors, hypoglycemia secondary to the exaggerated postprandial hyperglycemia, and occasionally secondary to disturbed intestinal absorption. The postgastrectomy syndrome was caused by a sequence of these early mechanical and late chemical factors, exaggerated by distinct psychoneurotic stigmas. Many of these individuals were stomach conscious. The shock of the operation, the postoperative course, later the postgastrectomy symptoms, and finally the diminished physical and mental resistance associated with underweight and malnutrition exaggerated the stomach awareness. The ultimate effect was a conflict between the postprandial symptoms, the late manifestations of which were relieved by food, and the fear to eat. The treatment of these patients presented a series of difficult clinical, nutritional and psychological problems, all of which required consideration.

Relative Deficiency of Parasympathomimetic Activity in Aqueous of Eyes with Chronic Simple Glaucoma. S. BLOOMFIELD. Arch. Ophth., 37: 608, May, 1947.

The aqueous humor was withdrawn by paracentesis from 20 eyes with chronic simple glaucoma, and 20 non-glaucomatous eyes with various other conditions. The fluid was then subjected to bioassay for parasympathomimetic activity utilizing the isolated frog heart technique. In 17 of the 20 non-glaucomatous eyes, appreciable amounts of parasympathomimetic activity was found present. This parasympathomimetic activity was inhibited by atropine, proving it to be due to the presence of acetylcholine. In all eyes with chronic simple glaucoma, parasympathomimetic activity of the aqueous was either absent or distinctly less than that found in the 17 non-glaucomatous eyes. Successful operation

did not alter this apparent deficiency of acetylcholine in the aqueous of glaucomatous eyes. The significance of these findings in the pathogenesis and therapy of glaucoma is discussed.

Right-Sided (Regional) Colitis. B. B. CROHN, J. GARLOCK AND H. YARNIS. J. A. M. A., 134: 334, May, 1947.

This type of segmental right-sided colitis occurs in about 8 per cent of our experience of 600 cases of ulcerative colitis. This form of colitis is most common in the cecum and ascending colon, progresses distally, frequently stopping at the sigmoid or recto-sigmoid angle. The symptoms are those of ulcerative colitis except that the sigmoidoscopy is entirely negative. No etiological factor is known. Peri-anal and peri-rectal fistulas are very common. The focal infection involving the joints, cardiac complications and eye complications in the nature of uveitis, iritis and corneal ulcer, occur with frequency. A small percentage of cases improve under conservative treatment and are cured. The majority of the cases require a second stage operation in the form of an ileo-sigmoidostomy followed some time later by a colectomy.

Office Procedure in Applying Penicillin Therapy to Acute Suppurative Bartholinitis. M. A. GOLDBERGER AND L. S. LAPID. New York State J. Med., 47: 984, May, 1947.

Three patients with acute Bartholin abscesses were treated by simple needle aspiration and re-injection of 100,000 to 200,000 units of penicillin in 10 cc. of physiological saline. One patient received one injection of 100,000 units of penicillin and required another aspiration and injection of 200,000 units of penicillin within 24 hours. In the other 2 patients, the abscesses were aspirated once and injected with 200,000 units of penicillin. Within 48 hours there was no evidence of any inflammatory process in any of the patients so treated. This method of treatment is recommended for its simplicity and because of the immediate relief obtained.

Acute Coronary Artery Diseases. History, Incidence, Differential Diagnosis and Occupational Significance. M. MASTER. Am. J. Med., 2: 513, May, 1947.

Acute coronary artery diseases have existed for hundreds, probably thousands of years. The arteriosclerosis observed in Egyptian mummies was of the same nature as is the disease today. The incidence of acute coronary insufficiency is of equal magnitude and significance as that of acute coronary occlusion. In fact, in case of acute, sudden, unexpected death, acute coronary insufficiency is observed more frequently than is the acute complete obstruction. We believe that the outlook for a patient recovering from an attack of acute coronary occlusion may justifiably be regarded more hopefully than it has been in the past.

The Synergism of Anesthetics and Hypnotics with Curare and Curare-like Alkaloids. E. P. PICK AND G. V. RICHARDS. J. Pharmacol. & Exper. Therap., 89: 1, May, 1947.

Premedication of mice and cats with small doses of ether, phenobarbital sodium, or pentobarbital sodium enhances the sensitivity of the animal to d-tubocurarine chloride, strychnos curare (Merck), dihydro- β -erythroidine hydrobromide and quinine methochloride or quinine ethochloride but not to quinine salts. Sub-effective amounts of these curare-like alkaloids have a paralyzing effect on mice and cats so premedicated. The effective doses of curare and the curare-like alkaloids for the pretreated animals are $\frac{1}{10}$ to $\frac{1}{2}$ of the dose necessary to produce a similar paralyzing effect in untreated animals. There is a reciprocal relationship between the amounts of the alkaloids and hypnotics necessary to produce this synergistic effect. Premedication with urethane, papaverine hydrochloride or scopolamine hydrochloride produces no distinct sensitivity of the aforementioned curare-like alkaloids. Pretreatment with morphine increases the effect of these curare substances in mice, but produces only a doubtful effect in cats and rabbits. *Subcutaneous* administration of curare and the curare-like alkaloids produced sensitization in mice, but not in cats. In this latter species *intravenous* injection of curare is highly effective. Premedication with anesthetics (ether) or hypnotics (barbiturates) followed by injection of curare alkaloids seems to be justified from a practical point of view since it produces an increased sensitivity to the curare drugs and thus permits attainment of a degree of muscular relaxation which cannot be obtained with the same amount of curare alone.

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THE CLINICAL IMPLICATIONS OF THE SHWARTZMAN PHENOMENON*

BERNARD BLACK-SCHAFER, M.D.

(Assistant Professor of Pathology, Duke University, Durham, N. C.)

INTRODUCTION

The phenomenon of local tissue reactivity and its potentialities was first recognized by Gregory Schwartzman of the New York Mount Sinai Hospital around 1928. Since that time numerous studies have been made on the phenomenon and its possible relationship to disease, both natural and experimental (1). The reaction commonly known as the Schwartzman phenomenon may be divided into two forms, the local and the general.

The local reaction is a hemorrhagic necrotizing lesion of skin produced by the intradermal deposition ("preparation") of a potent inoculum of bacterial toxin followed 24 hours later by an intravenous injection ("provocation") of a similarly potent toxin. Within 3 hours the phenomenon manifests itself at the inoculated skin site.

The generalized reaction is elicited by two intravenous injections of potent material 24 hours apart. Its hallmark is bilateral cortical renal necrosis. The rabbit is the animal universally used for these experiments. No other readily available laboratory animal is so well adapted to the production of this phenomenon, either general or local.

The source of the Schwartzman toxin is usually *Neisseria meningococcus* or *Salmonella eberthella*. Many other microorganisms, however, possess the ability to produce the toxin. Washed organisms living or dead are likewise capable of preparing and provoking the reaction. In addition, an antigen antibody reaction, *in vivo*, or its *in vitro* products may provoke the typical local phenomenon at skin sites prepared by the injection of a suitable bacterial filtrate.

Regardless of the source of potent toxins, they may prepare or provoke the local or general reaction nonspecifically, i.e., the skin may be prepared with meningococcal toxin and provoked with typhoid toxin or *vice versa*. It is apparent that a phenomenon capable of production by the products of a large number of common pathogenic and nonpathogenic bacteria and requiring a period of incubation measured in hours may play an important primary or secondary role in human disease.

LOCAL REACTION

Local hemorrhagic necrotizing cutaneous lesions occurring in conjunction with skin testing or serum therapy have been commonly described as examples of the

* From the Department of Pathology, Duke University School of Medicine, Durham, North Carolina.

Presented as one of the series lectures on recent advances in pathology and bacteriology at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, April 6, 1949.

Arthus phenomenon. A few authors (2, 3, 4) have recorded similar lesions as Schwartzman reactions. There are those who have felt that possibly the Arthus phenomenon does not occur in man and that all extensive cutaneous hemorrhagic reactions at the site of antigen injection should be considered examples of the local Schwartzman reaction (4). A mechanism suggested in explanation of the pathogenesis of the severe hemorrhagic necrosis of skin is as follows: An individual suffering from an overt or cryptic infection, at the same time hypersensitive to some substance not necessarily related to the infection (horse serum), is inoculated with the homologous antigen [i.e., horse diphtheria antitoxin (2)]. At the site of inoculation an allergic inflammation may occur of lesser or greater extent and intensity into which, because of increased capillary permeability, circulating toxins or bacteria may be selectively concentrated, thus "preparing" the tissues. The lesion may be provoked several hours to days later by the liberation into the blood stream of bacteria or their toxins from the original infection site or by the reintroduction of more antigen which, combining with its antibodies, provokes the previously prepared area.

Since the Arthus phenomenon is elicited by intradermal injection of antigen into a hypersensitive subject and, when severe, may present a hemorrhagic necrotizing focus surrounded by a larger area of erythema and edema similar to a Schwartzman reaction, it becomes apparent that the differentiation of the two phenomena may be difficult.

The histologic differentiation is not reliable. It is true that the Schwartzman reaction is reflected by necrotizing thrombophlebitis and arteritis as well as hemorrhage and eventual necrosis of the dermis and epidermis; however, the same is true, although usually to a lesser degree, of the Arthus reaction. While the latter experimentally is less severe than the former, the occasional hypersensitive individual may react maximally to a dose of antigen and thus produce all the changes qualitatively characteristic of the Schwartzman reaction. This is pointedly illustrated by the idiosyncratic individual who experiences an unusual and often fatal anaphylactic shock.

Despite the above objections to the interpretation of hemorrhagic necrotizing cutaneous reactions in hypersensitive individuals as Schwartzman reactions, the fact remains that such lesions commonly occur during acute infections and not in the course of prophylactic therapy. Furthermore, the experimentally proven ability of Schwartzman provocation by antigen-antibody reaction products is impressive evidence in support of the Schwartzman phenomenon thesis.

Recent unpublished work (5) in our laboratory has circumscribed the problem, permitting a direct attack upon the alternates, Schwartzman or Arthus phenomenon. When potent meningococcal toxins are mixed with purified beef gamma globulin and inoculated intradermally into previously untreated rabbits at weekly intervals the cutaneous reactions to the second and subsequent injections are large, hemorrhagic, and necrotizing. In contrast, the earliest hemorrhagic Arthus reaction (globulin control) appeared in one animal only after the third inoculation and compared to the aforementioned was insignificant. Even after the fourth injection the Arthus reactions were not comparable. The Schwartz-

man toxin control produced at no time lesions even reminiscent of those elicited by the mixed materials.

If the hemorrhagic reactions are not examples of the Arthus phenomena, and there is much to indicate they are not, then the most probable explanation is that the local reaction of antigen and antibody has provoked characteristic Shwartzman reactions prepared by the simultaneously inoculated meningococcal toxin. In any event it is apparent that the bacterial toxin has profoundly altered the tissue reaction to the antigen.

This production of large hemorrhagic necrotizing cutaneous reactions solely by means of intradermal inoculations of small amounts of antigen (1.5 mg. beef gamma globulin) and 0.05 cc. undiluted meningococcal toxin via the mechanism of the Shwartzman phenomenon is good evidence that similar reactions, in man, may indeed represent Shwartzman phenomena provoked by anaphylactic reactions.

GENERALIZED REACTION

The fully developed generalized Shwartzman reaction, in rabbits, is invariably fatal. However, there are various degrees of severity. Some animals, which survive the experiment, when sacrificed, reveal the presence of individual nephron necrosis (6) and little else to indicate a severe systemic reaction. Focal hepatic necrosis, subserosal petechial hemorrhages, as well as occasional adrenal hemorrhage and necrosis may accompany the fatal generalized Shwartzman reaction. Many of the animals succumb to the second intravenous injection too soon to manifest recognizable evidence of tissue damage. In our experience most animals surviving the provocative dose by 12 hours or more show cortical renal necrosis.

Occasional reports, in man, of a fatal sequel to two or more intravenous injections of typhoid vaccine given 24 hours apart have appeared with the appellation of "Sanarelli-Shwartzman phenomenon" (7, 8). In none of the cases referred to was the characteristic experimental kidney lesion found, although one patient (8) survived three days. The absence of renal cortical necrosis in man need not imply the absence of the Shwartzman reaction. Those working with rabbits are acquainted with the ease with which the kidneys develop the lesion. The experience of Trueta and his group (9) is a point in hand. Certainly, the lesion in man is a rarity despite the ubiquity of infection and shock of all varieties, which according to these workers readily evokes the change in rabbits.

The hepatic necrosis, petechial serosal hemorrhages and vague references (7, 8) to kidney injury described in the patients do not constitute sufficient evidence to establish the diagnosis of a generalized Shwartzman reaction on morphologic grounds. Yet the obvious relationship of the profound reaction to two intravenous injections of typhoid organisms is inescapable, and it would appear good practice to be aware of the fact that two intravenous injections, 24 hours apart, of typhoid vaccine or any other Shwartzman potent material may lead to a serious and sometimes fatal systemic reaction, possibly *via* the mechanism of the generalized Shwartzman reaction.

BACTERIAL CUTANEOUS PURPURA

Infectious diseases are occasionally complicated by cutaneous purpura. An excellent example, which because of its increased incidence during the late war is still fresh in our minds, is meningococcemia. When complicated by adrenal hemorrhage and necrosis, the complex is widely known as the Waterhouse-Friderichsen syndrome. Occasional staphylococcal, streptococcal, pneumococcal and influenzal bacteremias give rise to a similar clinical and pathologic picture. More frequently, however, the cutaneous purpura is unaccompanied by adrenal lesions. It was suggested sometime ago by Schwartzman that these phenomena might represent a form of "local tissue reactivity." Experimental confirmation of this was advanced by Black-Schaffer, Hiebert and Kerby in 1947 (6). They demonstrated that repeated intravenous inoculation of washed meningococci resulted, in the same animal, in the production of bilateral renal cortical necrosis, in the provocation of hemorrhagic reaction at the site of an intradermal inoculum of washed meningococci, and in a generalized cutaneous purpura. In addition, in one animal, massive hemorrhagic necrosis of the adrenals was found at autopsy. This experimental reproduction of meningococcemic purpura and the Waterhouse-Friderichsen syndrome in conjunction with the localized and generalized Schwartzman reaction lends strong support to the view first propounded by Schwartzman. It is highly probable that in man as in the rabbit the lesions are prepared and provoked by the lodged and circulating meningococci and their toxins.

Prompt sulfonamide and antibiotic treatment of meningococcemia is highly successful. Still, some patients with very fulminating disease die. It would appear that a helpful adjunct in the treatment of bacterial purpuras might be antiserum prepared not only against specific organisms but directed likewise against the Schwartzman toxin. Such antisera would in all probability possess a marked detoxifying effect and might reduce the number of deaths from Schwartzman potent bacteria.

SECONDARY INFECTIONS

Numerous disease entities are characterized by hemorrhagic and necrotizing complications. An example is smallpox [*variola hemorrhagica pustulosa* (10)]. Almost invariably such complications appear coincidental with or following secondary bacterial infections. The Schwartzman phenomenon has been proposed as the mechanism leading to these changes. The regular provocation of the reaction prepared with the products of one organism by the potent material of any of a number of other organisms plus the hemorrhagic necrotizing character of the reaction presents the background for the suggestion.

In the case of smallpox, Gratia and Linz (11), confirmed by Koplik (12), demonstrated that vaccinia lesions in rabbits became hemorrhagic upon intravenous injection of *Escherichia coli* filtrates.

Perhaps the best example of what may be a generalized Schwartzman reaction provoked by secondary bacterial invaders following upon a primary viral infection is found not in man but in swine. Hog cholera caused by a virus may run a benign course until secondary bacterial infection provokes a necrotizing

pneumonia and in some animals bilateral cortical renal necrosis (13). Schwartzman (14) has suggested that the explanation for the fatal hemorrhagic necrotizing pneumonia complicating epidemic influenza, in man, may be another example of viral and bacterial synergism. Indeed, Witebsky and Salm (15) have demonstrated the ability of *Hemophilus influenzae*, living or dead, both to prepare and provoke the classical Schwartzman reaction.

ULCERATIVE COLITIS

The pathogenesis of specific organ disease has been ascribed to the Schwartzman phenomenon. Winkelstein and Schwartzman (16, 17) interpret nonspecific ulcerative colitis as a provocation by *Escherichia coli* toxins of a previously injured ("prepared") large bowel. The preparatory agent may be a member of the Salmonella group or any organism capable of elaborating potent toxins. The *E. coli*, natural inhabitants of the bowel, could "provoke" such an inflammation, lending to it a necrotizing hemorrhagic aspect. This thesis was put to a limited therapeutic test by Winkelstein and Schwartzman. They treated a small but gravely ill group of patients with concentrated antitoxin prepared against *E. coli* and the Schwartzman factor. Excellent results were achieved in 70 per cent of the group. Further investigation of this promising therapeutic tool is still in progress.

EXPERIMENTAL TUMOR THERAPY

The Schwartzman phenomenon plays an important role not only in the realm of immunology and infectious disease but also in the therapy of experimental tumors.

It was not long after Schwartzman's basic publications that Gratia and Linz (18) discovered the effects of the active substance of *E. coli* filtrates upon transplanted liposarcoma in guinea pigs. The tumors underwent prompt hemorrhagic necrosis without similar lesions elsewhere. The same selective necrosis of tumor was also achieved with a single intravenous inoculation of filtrate. This experiment has since been confirmed and amplified by many, notably Shear and his group (19). These last have undertaken numerous chemical studies resulting in the concentration from filtrates of *Serratia marcescens* (*Bacillus prodigiosus*) of a polysaccharide which in minute doses may cause hemorrhagic necrosis of large sarcoma masses. The polysaccharide is capable of preparing and/or provoking the Schwartzman phenomenon in rabbits and is closely related immunologically to the active principle of crude *Serratia marcescens* filtrates (20). While this approach to the therapy of cancer remains as yet in the stage of experimentation, it finds its roots in clinical observations on induced erysipelas by Fehleisen (1883), which were further investigated in the United States by Coley (21). The latter prepared a mixture of *Serratia marcescens* and *E. coli* toxins which, like erysipelas itself, could cause regression in the size of malignant tumors and is recorded as having effected numerous remarkable cures of proven cancers (23). Upon close scrutiny it would appear highly probable that Gratia and Linz had rediscovered Coley's toxin therapy. In the light of Schwartzman's basic researches it is probable that the phenomenon of local tissue reactivity and the provocation of hemorrhagic necrosis of cancer tissue are closely related phenomena elicited by identical bacterial products.

The means by which tumor necrosis and cure, in some animals and humans, is brought about remains, to date, a mystery. Andervont (24) and Gerber and Bernheim (25) state their belief that the toxic bacterial substance acts directly upon the tumor cells. The latter emphasize the absence of any notable vascular changes in regressing tumors such as characterize the local Shwartzman reaction. Despite this, it is significant to note that Thomas and Stetson (26) have recently demonstrated the interesting provocative effects of papain and thiol compounds (cysteine, BAL) in eliciting Shwartzman-like reactions in rabbits prepared by one intravenous inoculation of potent meningococcal filtrate. In addition they could block the phenomenon by application of bromobenzene (lipoid solvent) to the prepared cutaneous site. They suggested that the Shwartzman phenomenon may be produced by activation of a tissue protease or by withdrawal of a protease inhibitor. If this be confirmed, then it becomes apparent that the re-investigation of protease content of tumor cells and tumor capillaries may furnish a key to the pathogenesis of the tumor necrosis described by Gratia and Linz. Such an approach may explain why Coley's toxin and Shear's polysaccharide are effective against some sarcomas and relatively inactive against most carcinomas. Limiting the use of these therapeutic agents to certain tumor types may thus provide a means of assaying their place and value in the treatment of cancer.

Beeson (27) performed a significant experiment illustrating, at least in part, the mechanism of natural and acquired immunity of the rabbit to the Shwartzman phenomenon. Animals either naturally refractory to the reaction or made so by the repeated production of the local reaction reacted maximally if, before the intravenous provocation, the reticulo-endothelial system was blocked by thorotrast. The explanation advanced was that the temporary blockade made possible the delivery of the intravenously administered toxin to the site of preparation. In short, natural and acquired immunity is, in this experiment, a function of the reticulo-endothelial system. To what degree similar treatment of cancer-bearing animals may affect cancer necrosis and rate of cure await experimentation. At any rate Beeson has succeeded in unlocking still another approach to the problem of the Shwartzman phenomenon.

CONCLUSION

Man living in and encompassing a complex environment is subject to attack by many agents. When disease is established, the chain of kinetic forces constituting our protective device is impaired, permitting effective action of still further detrimental agents. Undoubtedly much of our difficulty in solving medical problems arises from the complex nature of disease etiology. The Schwartzman reaction is a tool enabling the investigation of some of these multiple etiologies.

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MASSIVE CEREBRAL HEMORRHAGE FOLLOWING HEPARIN THERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS

REPORT OF TWO CASES WITH A REVIEW OF THE LITERATURE¹

SIDNEY M. COHEN, M.D.

Heparin has been used for several years as an adjuvant to chemotherapy and the antibiotics in the treatment of subacute bacterial endocarditis. Clinical experience, however, has shown that treatment with anticoagulants in this disease does not give any better results than when the bacteriostatic drugs are used alone. Moreover, the use of heparin has been found to be hazardous because of the increased bleeding tendency induced by therapeutically adequate doses, as shown by the high incidence of cerebral hemorrhage following heparinization in subacute bacterial endocarditis. Such clinical and pathological observations are significant in their bearing on the anatomical factors involved in the production of spontaneous massive cerebral hemorrhage. However, since the therapeutic possibilities of this physiological agent in its capacity of rendering the circulating blood incoagulable are many, heparin has continued to be used in many thrombotic and embolic disorders. Thus it seems worthwhile to review briefly the discovery of the substance, its relationship to mast cells, its chemistry, physiology, and clinical applications.

During a study of the phosphatides cuorin and jecorin in heart muscle and liver, Jay McClean (1), in 1916, while working in Howell's laboratory, isolated a substance which appeared to act in a manner opposite to that of cephalin or thrombokinase: it retarded coagulation instead of accelerating it. Up to this time no anticoagulant was known to exist in mammalian tissue and Howell (2), in 1922, was first to succeed in the production, in quantity, of the first heparin from dog liver—hence its name.

Physiologic studies of this substance in the experimental animal were at first limited because of its toxicity. In the dog, when the clotting time was increased to 30 minutes it produced muscle weakness and vomiting. With larger doses there occurred profuse intestinal hemorrhages, and autopsy revealed multiple hemorrhages in all the organs and beneath all serous membranes (3). Charles and Scott (4) of the Connaught laboratories obtained, in 1929, purified heparin as a crystalline barium salt. This was free of the toxic properties of the original crude product and 100 times as potent. In a series of animal experiments, begun in 1932, in the Department of Surgery of the Toronto General Hospital, it was disclosed that heparin prevents thrombosis resulting from mechanical and chemical injuries to veins. Murray and Best (3), in 1938, reported greater success in arterial anastomoses and cross-suturings of blood vessels in heparinized animals and facilitation in the transplantation of organs. Experiments involving cross-circulation exchange transfusion, whereby the blood of a donor clears the blood

¹ From the Laboratories, Division of Neuropathology, The Mount Sinai Hospital, New York.

of a recipient with renal insufficiency of metabolic end-products, also have been greatly facilitated [Thalheimer, Solandt and Best, 1938 (5)]. The application of this technique of reciprocal blood transfusion in man has been reported by Duncan and coworkers (6) in 1940.

The original "Howell unit" represented the amount of heparin activity which will prevent clotting of 1 cc. of cold cat's blood for 24 hours. A unit is at present defined by the Toronto workers as the activity of 0.01 mg. of pure heparin, i.e., of a crystalline barium salt of heparin set aside for this purpose at the Connaught Laboratories in Toronto. This unit contains 500 Howell cat units per milligram.

Mast cells. In 1937, Jorpes, Holmgren and Wilander (7) showed by means of the metachromatic staining reaction with toluidine blue that heparin is produced by the mast cells of Ehrlich. In 1877, Ehrlich (8) introduced the name, mast cell, for a category of connective tissue cells whose granules stained metachromatically with aniline dyes, in a tone different from that of the dye employed. In this way he separated them from the ordinary Waldeyerian plasma cell. He considered the mast cells as overnourished connective tissue cells, hence the term "mast" (German: fattening). He also maintained that the blood mast cells represented bone marrow derivatives. In recent years hematologists held to the view that the mast cells of the blood and those of the connective tissue are two unrelated types. The former they regard as mast leucocytes or basophiles, while the latter are referred to as tissue, or histogenous, mast cells. In the early embryo no apparent morphological differences exist between blood mast cells and tissue mast cells, since both types take origin from a common mesenchymal cell, the resting wandering cell of Saxer. The histogenous mast cell, a distinctly connective tissue cell, is characterized by marked variations in number and cytoplasmic contours. It has fine and coarse granules and a relatively small nucleus, which is generally round or oval, rarely lobulated. In the adult, these cells are derived by mitotic division from preexisting tissue mast cells and by an elaboration of mast granules in various types of connective tissue cells, as lymphocytes, plasma cells, clasmatoocytes, adventitial cells and histiocytes. Very slow amebism can occasionally be observed. In order of their abundance the tissue mast cells have their habitat in mesentery, peritoneum, subcutaneous tissue, intermuscular tissue, spleen, gut, lung, bone marrow, liver and kidney. During acute inflammatory conditions the tissue mast cells are invariably decreased in number. For some unknown reason the cells undergo rapid disintegration, the freely distributed granules being phagocytosed by neighboring polyblasts. In contrast to acute inflammation, the chronic variety is always accompanied by a marked numerical increase of tissue mast cells. They are distributed throughout the body tissues around capillaries and small blood vessels without a muscular coat. Because of their perivascular position they are able to void their granular contents into the peripheral tissue juices or almost directly into the blood stream. This indicates that these cells may have a physiological function, constituting a hormonal system.

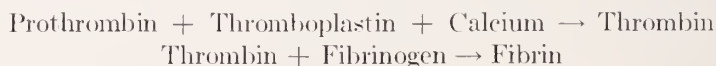
Evidence of the capacity of the mast cells to secrete heparin has been supplemented recently. This was based on the increase in the mast cell content in the

tissues of the victims of Hiroshima, associated with a general bleeding tendency in these patients. Similarly a condition of hyperheparinemia has recently been produced by Garrott Allen in Chicago through roentgen ray irradiation of dogs. Significant also is the observation that in urticaria pigmentosa, where multiple petechial hemorrhages are found in the skin, there are abnormal local accumulations of mast cells.

Oliver (11) investigated the mast cell tumors of the skin of dogs in order to examine their role on heparin formation. He found that the mast cell tumor contained 50 times as much heparin as has been obtained from the richest normal source of the most active form of heparin (dog liver). The immature tumor contained less heparin than the mature tumor. In the immature cell of the more malignant tumor the particulate matter is recognized in the living cells as grayish, ill-defined particles or as a weakly metachromatic, fine granulation in the stained preparation. In the mature cells of a relatively benign mast cell tumor, both in the living cell and in stained preparations, the particulate matter occurred in the form of discrete, dense, and strongly metachromatic granules, resembling those of the normal mast cell. Since there may be a great amount of grayish particulate matter or fine stained granules in a tumor of a relatively low heparin content, he suggested that this material presented an early or precursor phase in the development of heparin. Paff (12) cultivated neoplastic mast cells *in vitro* and showed that the cytoplasmic granules varied in size, number, and staining properties.

Chemistry. The chemical structure of the active substance in heparin is not known. It is doubtful whether any homogeneous, pure samples of heparin have ever been prepared. Heparin has been identified as a mucopolysaccharide, resembling chondroitin sulfuric acid of the cartilage. Samples of the most potent heparin were found to contain about 26 per cent of a uronic acid and about 23 per cent of glucosamine, these components together making up about 90 per cent of the organic skeleton of heparin. It also contains three groups of ester sulfuric acid to each disaccharide unit. Many polysaccharides acquire anticoagulant properties when esterified with sulfuric acid. Because of its high content of ester sulfuric acid, heparin is said to have the strongest electrical charge of any organic compound in the body (10).

Mode of action. According to the classical concept of Morawitz, Fuld, and Spiro (13), blood coagulation occurs in two stages:



Heparin acts in three distinct ways to prevent the above reaction (14): by impeding the agglutination and disintegration of platelets, it prevents the liberation of thromboplastin, and therefore blocks coagulation in the very first phase; it prevents the conversion of prothrombin to thrombin with the aid of serum albumin; it forms a strong antithrombin with serum albumin.

Albert Fischer (13), in 1931, expressed the view that heparin produces its effect by displacing the isoelectric point of the prothrombin and other blood

proteins. He regarded the heparin effect as a purely physicochemical phenomenon caused by a high molecular colloid endowed with a strong electronegative charge. This view was corroborated by Chargoff and Olson (15) who found that protamine, a simple protein with basic properties, combines with heparin, the resulting compound being free from anticoagulant action. Protamine sulfate, 50 to 100 mg., injected intravenously in man in a 1 per cent sterile solution, instantaneously brings the coagulation time of the blood down to normal. The basic dye, toluidine blue, also neutralizes the electric charge of heparin and inhibits its activity. It is also known that the interaction between heparin and thrombin is reversible and very loose. When thrombin and heparin are present in suitable proportions to maintain the fluidity of a sample of blood, the addition of thromboplastin causes coagulation. Heparin has a multiple effect, acting not only on the coagulation system, but also on many other systems (13). It neutralizes serum complement, interfering in the Wassermann reaction. It influences the sedimentation rate of the red blood corpuscles. In spite of a strong ionic dissociation, heparin exerts an extremely low osmotic pressure in an aqueous solution. This phenomenon involves a protective mechanism, preventing disruption of the heparin-producing cells by water entering from the outside in order to establish osmotic equilibrium. The sodium and potassium ions bound to the high molecular negative complexes of heparin do not exert any osmotic pressure. This lack of osmotic pressure makes heparin useful in blood analysis because it does not cause shrinkage of the red blood corpuscles. A concentrated 5 per cent solution can safely be injected undiluted into the blood.

Clinical applications. Crafoord in Sweden and Gordon Murray (16) in Canada, simultaneously and independently showed (1935-1942) that thrombosis can be prevented if heparin is given in sufficient amounts, 250 to 325 mg. a day, until the patient is out of bed. Murray and Best (3) in 1938, and Murray and Mackenzie (16) in 1939, reported on a number of cases of spontaneous thrombophlebitis and pulmonary embolism treated with heparin. Since then, excellent results in these conditions have been reported by many investigators. Heparin has been reported to be useful in arterial suture, venous graft, mesenteric thrombosis, splenectomy, blood transfusion, embolectomy, thrombosis of the central vein of the retina, coronary thrombosis, thrombosis of the posterior inferior cerebellar artery, and cavernous sinus thrombosis (17).

Knisely and coworkers (18) found in 600 unanesthetized patients' diagnosed as having a wide variety of disease conditions, that the blood cells in the bulbar conjunctiva agglutinated into masses; this changed the blood from its normal, relatively fluid, state to a circulating "sludge." Completely unagglutinated blood has been found thus far only in strictly healthy animals and men. They offered the following observations: "1. The resistance of sludged blood to its own passage through the bottlenecks of the circulatory system forcibly reduces the rates of blood flow through all the open vessels of the body. 2. Agglutinated red cells are ingested and destroyed in the phagocytic cells of liver and spleen. 3. There is settling and sedimenting of masses of agglutinated blood cells out of the moving blood plasma during life. Various degrees of reduction of circulating

blood volume caused by mechanisms 1 and 2, above, initiate intermittent, prolonged, controlled shutting off of the arterioles of a selected series of tissues and organs. These effects may play an important role in producing thromboses, various anemias, and may also have a cumulative effect in the aging process." The authors state that "as we learn how to keep blood normally unagglutinated and fluid, vessel walls intact, normal red cells from being destroyed, and adequate blood volumes present, many effects of other pathologic mechanisms will stand out clearly, unobscured by the sludge mechanisms. Heparin, by rendering the circulating blood incoagulable, should be very useful in the study and prevention of pathological alterations produced by circulating sludge."

Heparin in subacute bacterial endocarditis. Friedman, Hamburger and Katz (19), in 1939, introduced the combined heparin and sulfapyridine therapy for subacute bacterial endocarditis. Heparin was added on the theory that it would prevent new fibrin and platelet formation and might allow the valve to repair itself. One of their patients died of a cerebral hemorrhage. Kelson and White (20) then reported a series of 7 cases treated in the same way. The object of the heparin was to restrict the nidus and culture medium for bacterial growth, to prevent embolism from the freeing of fresh thrombus, and to check the growth of the vegetations so that proliferating fibroblasts might fill in the area thus limited. They too reported a case of death due to cerebral hemorrhage. This new method was also tried at The Mount Sinai Hospital in 1939, and in two instances cerebral hemorrhage and death occurred. These two cases are herein reported.

CASE REPORTS

Case 1. History (Adm. #488271, P.M. #11330). The patient, a man aged 28 years, entered The Mount Sinai Hospital on November 4, 1939 after an acute illness of two weeks' duration. The illness was marked by fever, generalized muscle pains, fatigue and frontal headaches. In addition he complained of slight pain in the left thumb and in both knees. He was given sulfanilamide for four days prior to his admission to the hospital. This was stopped when he developed cyanosis of the finger nails. He had acute rheumatic fever at the age of 14 and was told that he had a heart murmur. For nearly seven years before the onset of the recent illness he was free of symptoms except for occasional palpitation.

Examination. The patient was a thin, young man who was mentally clear and cooperative. Temperature was 102°F.; pulse, 108, regular; respirations, 22 per minute; blood pressure, 136 systolic and 50 diastolic. There was an erythematous, macular eruption over the nose and cheeks, in butterfly formation, and also over the anterior chest. There were petechiae on the left conjunctiva and over both legs. The heart examination disclosed aortic insufficiency and mitral stenosis. There were no positive neurological findings.

Laboratory data. White blood count, 14,900, with 80 per cent polymorphonuclear leucocytes; red blood count, 4,840,000; 88 per cent hemoglobin. Urine was negative except for an occasional red blood cell. Sedimentation time was 30 minutes. A blood culture grew *Streptococcus viridans*.

Course. The diagnosis of subacute bacterial endocarditis was made and the patient was given 6 Gm. of sulfapyridine daily. One week later intravenous heparin was instituted. The dosage was regulated so that the coagulation time remained at about one hour. After two days of treatment the patient became sleepy and developed weakness of the left leg. A cerebral hemorrhage was suspected and the heparin was discontinued. The patient lapsed into coma half an hour later. His pupils became fixed and unequal. A flaccid

paralysis of the upper extremities developed and bilateral sustained ankle clonus was elicited. Two hours later a lumbar puncture yielded clear fluid under increased pressure. The patient then had 3 or 4 generalized convulsions, developed respiratory failure and died less than an hour later, three hours after he lapsed into coma.

Postmortem findings. General, summarized. Subacute bacterial endocarditis (*Streptococcus viridans*) involving mitral valve and subaortic endocardium. Rheumatic heart disease: chronic interstitial aortic, mitral, tricuspid and pulmonic valvulitis. Aortic insufficiency (moderate) and stenosis (slight), mitral insufficiency (moderate) and stenosis (slight). Hypertrophy and dilatation of all chambers most marked in left ventricle. Focal fibrinous pericarditis over right auricle. Focal myofibrosis cordis (? old embolus). Numerous small renal emboli. Small recent splenic infarct. Petechiae in conjunctivae and skin. Congestion of lungs, liver, and spleen.

Brain. Gross. The brain was soft in consistency and the gyri were flattened, particularly over the right fronto-parietal and adjacent occipital lobes. In this area the brain was exceedingly soft and exhibited fluctuation. The right cerebellar hemisphere was definitely softer than the left and perhaps slightly larger. There was a small subarachnoid clot, about 1.0 by 0.5 cm., overlying the right posterior surface at the second cervical segment of the cord.

On sectioning, the brain showed marked asymmetry, with the right hemisphere, displaying marked swelling and deformity. Extending from about a point on the level with the foramen of Monro through the posterior part of the frontal, the entire parietal and into the anterior one-half of the occipital lobes there was a large defect on the upper one-half of the right hemisphere which was filled with a dark red, in part necrotic and in part solidified, mass (fig. 1). In certain parts this mass could be dislodged but in its midportion it showed attachments to some of the surrounding brain tissue. The defect was enveloped by a wide zone of softened tissue; some of that softening extended into the more ventrally situated parts of the brain, such as the corpus striatum and the internal capsule. The corpus callosum was also softened in the part adjacent to the defect. The ventricles were dislodged, the left being somewhat deformed. The right anterior horn was filled with a small quantity of partly solidified blood. The posterior horn of the right lateral ventricle contained a small quantity of blood.

Microscopic observation. Sections of the cerebrum stained with hematoxylin and eosin and by the Van Gieson method showed a massive accumulation of blood (fig. 2) surrounded by disorganized brain tissue. The blood showed little tendency to organization; it formed bands of densely aggregated red blood cells, surrounding spaces filled with serum in which there were some streams of red blood cells (fig. 3). This was in marked contrast to the usual appearance of extravasation encountered in the more common form of cerebral hemorrhage (figs. 4 and 5). The adjacent brain tissue showed areas of rarefaction and occasional extravasations. Here and there was a nodule of small round cell accumulation, probably outlining a blood vessel. A naked blood vessel was occasionally visible at the periphery of the hemorrhagic area. There were many well-preserved, naked blood vessels of varying dimensions.

Case 2. History (Adm. #448911, P.M. #11350). A married woman, aged 43 years, was apparently well until four weeks before entering the hospital when she began to have lower abdominal pain, diarrhea, malaise and fever. A physician noted a heart murmur. She then developed fleeting joint pains. Blood cultures taken at that time were positive for *Streptococcus viridans*. She gave a history of typhoid and malaria and a so-called "brain fever" in childhood. Ten years before admission she had an appendectomy and a uterine myomectomy, apparently without oophorectomy.

Examination. There was a blowing systolic murmur over the apex of the heart and no other general physical or neurologic findings. The temperature was 103°F.

Laboratory data. There was a persistent trace of albumin in an otherwise normal urine. Blood culture showed *Streptococcus viridans*. Red blood count, 3,800,000 with 69 per cent



FIG. 1. *Case 1.* Gross appearance and extent of the hemorrhage. (Photograph)



FIG. 2. *Case 1.* Appearance of the hemorrhage as seen with the unaided eye in a stained section. (Mallory stain, photograph, $\times 3$)

hemoglobin; white blood count, 6,100 with 70 per cent polymorphonuclear cells and 18 per cent lymphocytes.

Course. The patient was given sulfapyridine on admission, receiving about 7 Gm. a day. Within 24 hours her temperature returned to normal. Six days later intravenous heparin was started and the blood coagulation time was maintained at one hour. Ten days after admission she developed a flaccid paralysis of the right arm and a right Babinski sign. The right eyelid had less tone than the left. The eye tended to turn inward and upward

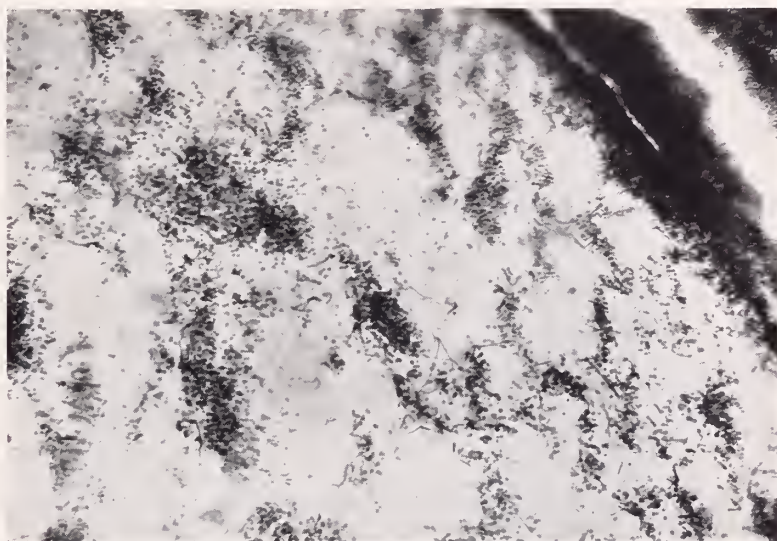


FIG. 3. *Case 1.* Section showing the character of the hemorrhage under higher magnification. (Mallory stain, photomicrograph, $\times 100$)

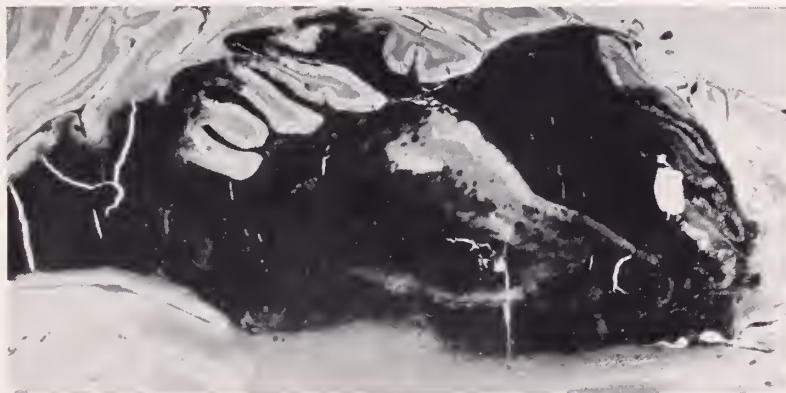


FIG. 4. Appearance of extravasated blood in spontaneous hemorrhage in a case untreated by heparin, as seen with the unaided eye in a stained preparation. (Photograph, $\times 3$)

when the eyes were opened. The patient became comatose and died four hours after the onset of neurologic manifestations.

Postmortem findings. General, summarized. Subacute bacterial endocarditis, mitral valve, *Streptococcus viridans*. Inactive rheumatic valvulitis of mitral? Fatty infiltration and cloudy swelling of ventricular myocardium. Subepicardial hemorrhages. Pericardial effusion. Pulmonary emphysema. Primary complex, right upper lobe. Swelling of hilar lymph nodes. Congestion and fatty infiltration of liver. Infectious splenic tumor with

older infarction. Congestion and cloudy swelling of kidneys with recent and older infarctions and hemorrhages into the pelvis and peripelvic fat tissue. Cholesterosis of gall-bladder. Status postcervical amputation of uterus and both adnexa with intrapelvic fibrous adhesions. Status post appendectomy.

Brain. Gross. The dura was bulging, particularly over the left hemisphere. On removing the dura, the left hemisphere appeared definitely larger than the right and its convolutions were flatter. Over-lying the superior part of the left parietal lobe was a thin subarachnoid collection of blood. The underlying brain tissue was discolored, purplish in color, suggesting a hemorrhagic tint. The entire left hemisphere was softened, particularly over the parietal lobe, where loose fluctuation was obtainable. There was another point of softening in the posterior part of the left occipital lobe. Despite gentle manipula-



FIG. 5. The appearance of the extravasated blood in the hemorrhage shown in Figure 4. (Photomicrograph, $\times 100$)

tion of the brain, the friable, softened left parietal cortex ruptured for about 2.5 cm. and a fragment of clot with attached pulpy brain tissue was extruded. The floor of the 3rd ventricle was bulging, but was firm in consistency. The optic tracts were flattened, particularly the left. The vessels were grossly normal.

On sectioning a number of hemorrhagic areas were noted (fig. 6): a large one in the left cerebral hemisphere extending from the anterior extremity of the genu of the corpus callosum all the way back to within 5 cm. of the occipital pole; it was largest at the level of the massa intermedia, where it extended almost throughout the entire vertical plane of the hemisphere and occupied the entire subcortex up to the internal capsule. Posteriorly, as it entered the posterior part of the parietal and adjacent occipital lobes, it was small in size and gave the appearance of softened tissue containing islands of extravasations. Another hemorrhagic area was found in the right hemisphere in the region of the superior frontal convolution at its posterior end. Another hemorrhagic area was found in the left thalamus, while still another was found in the vermis of the cerebellum; the last (and smallest) was noted near the left occipital pole. Areas of discoloration were also found in the midbrain and in the pons. Those found in the midbrain and the pons gave the impression of con-

glomerate pericapillary hemorrhage, probably secondary to the increased intracranial pressure, while the former, larger hemorrhagic ones were probably red infarcts or the late forms of encephalomalacia rather than frank massive hemorrhages. The ventricular system showed no free blood.

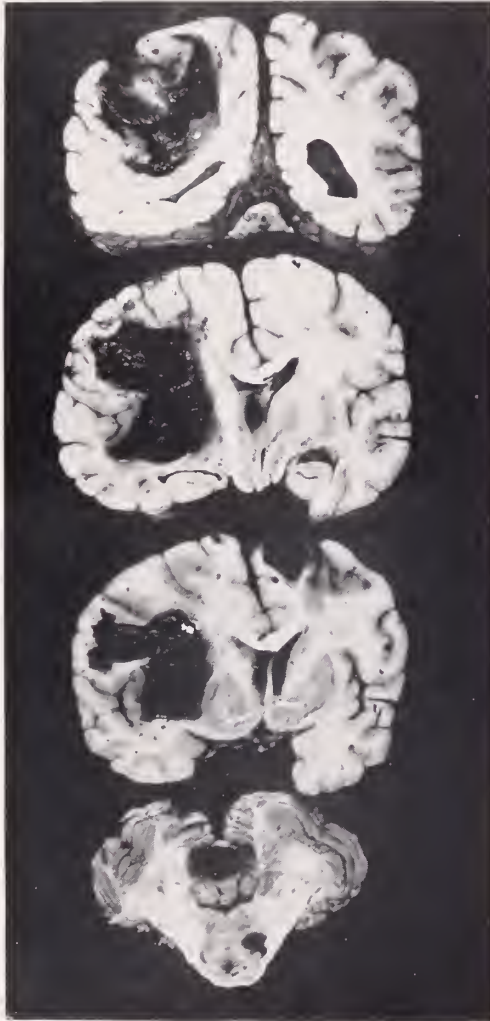


FIG. 6. Case 2. Gross appearance and extent of the hemorrhage. (Photograph)

Microscopic observations. Sections of the cerebrum stained with hematoxylin and eosin and by the Van Gieson method showed a massive accumulation of blood surrounded by slightly disorganized brain tissue. The blood showed little tendency to organization (fig. 7). As in Case 1, bands of densely aggregated blood cells bordered spaces filled with serum (figs. 7 and 8). The surrounding tissue showed areas of rarefaction and occasional extravasations. Here and there was a small nodule of small-cell accumulation, probably outlining a blood vessel. A naked blood vessel was occasionally visible at the periphery of a hemorrhagic area.

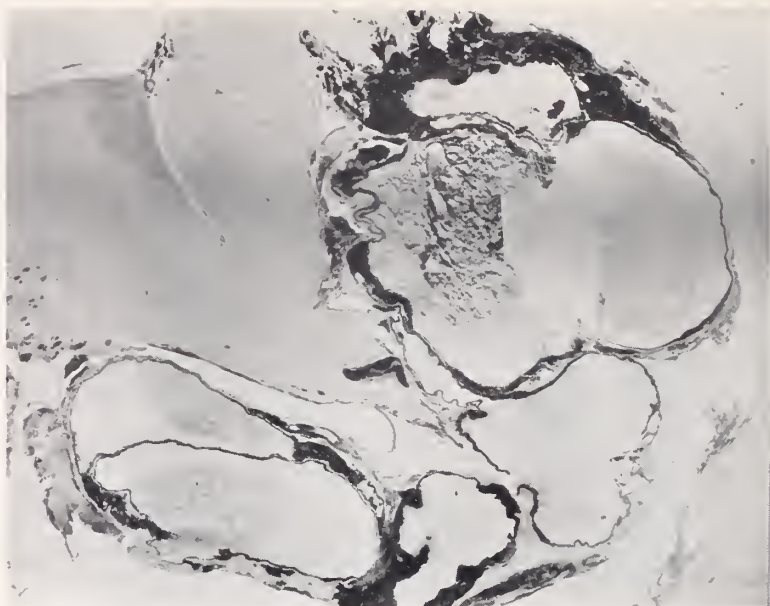


FIG. 7. *Case 2.* Appearance of the hemorrhage as seen with the unaided eye in a stained section. (Mallory stain, photograph, $\times 3$)

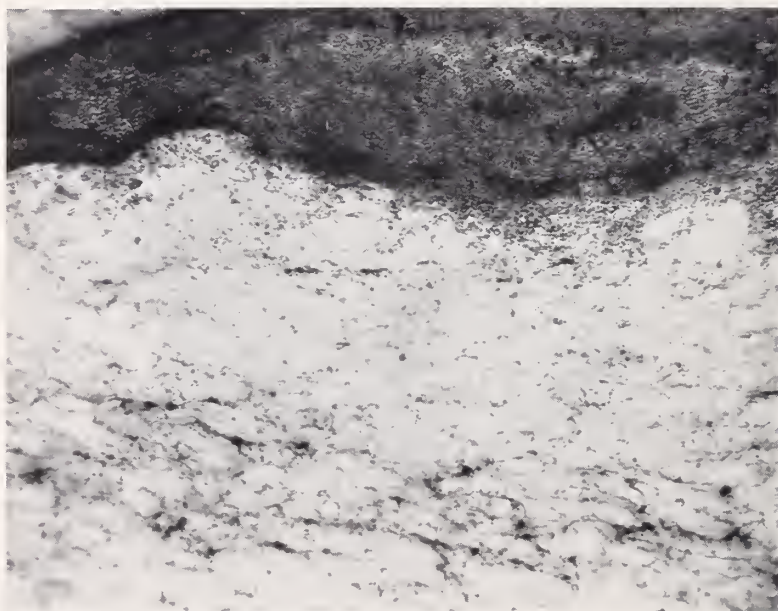


FIG. 8. *Case 2.* Section showing the character of the hemorrhage under higher magnification. (Mallory stain, photomicrograph, $\times 100$)

COMMENT

The pathological findings in the foregoing two cases were unusual in that the blood in the areas of brain softening tended to remain fluid and showed little

tendency to organize. This, it was felt, serves to support the explanation of the cause of these hemorrhages and might shed further light on the sequence of events preceding the more common form of spontaneous cerebral hemorrhage. With this in mind, 12 other cases with postmortem reports were found in the literature in which treatment of subacute bacterial endocarditis with either a combination of sulfapyridine and an anticoagulant or with heparin alone was followed by a cerebral hemorrhage. The coagulation time prior to death in these cases was 30 minutes or longer.

McClean's case (21) was the only instance in which a coagulation time of 7 minutes was reported. Cerebral symptoms appeared from 2 to 15 days after the initiation of anticoagulant therapy.

Kelson and White (21) reported a case of cerebral hemorrhage in which the neurological signs appeared five days prior to death. Heparin therapy had been given for 40 hours. Postmortem examination revealed large occipital and subdural hematomas. The authors believed that these were probably embolic and occurred spontaneously, although the drug very likely increased the hemorrhage and hastened death.

Friedman, Hamburger and Katz (19) reported a fatal case in which symptoms suggesting cerebral hemorrhage appeared on the day of death. Postmortem studies disclosed a hemorrhage in an area of preexisting encephalomalacia, which resulted from an infected embolus seven days earlier. The lateral, third and fourth ventricles were filled with blood and there was some blood in the subarachnoid space. They concluded that heparin may cause intractable bleeding, resulting from rupture of a blood vessel after embolization.

McClean's (21) first case had two cerebral accidents, three months and one month respectively prior to institution of heparin therapy. The patient died rapidly after appearance of blurred vision, decreased auditory acuity, headache, and urinary frequency. Brownish discoloration over the left parieto-occipital area was found at postmortem. There was an old hemorrhagic area (embolic infarct) at the midportion of the right middle cerebral artery. Subarachnoid edema with old hemorrhage was also present. His second patient developed neurological symptoms seven days before death. Then there developed headache, painful abdomen, involuntary voiding, spasmodic twitching of the left arm, occasional convulsive seizures and the patient died.

In Fletcher's (22) first case the patient died two hours after the onset of symptoms. There was a small subarachnoid hemorrhage in the occipito-parietal region, a hemorrhage in the left frontal lobe and also one in the left lobe of the cerebellum. He concluded from this case that in a patient suffering from disease in which emboli are common, to render the blood less coagulable is to run the risk of serious hemorrhage. In a second case of Fletcher's (23) death occurred two days after the onset of cerebral symptoms, although the heparin infusion was stopped six hours before death. The brain showed an extensive subdural hemorrhage on the right side, evidence of old subarachnoid hemorrhage and a mass of blood clot, exuding from the right occipital pole, which arose from a hemorrhagic cavity in the white matter. There were also a few cortical hemorrhages in this region. The microscopic studies of the brain revealed that near

the hemorrhage there was considerable proliferation of the capillary endothelium and irregular hemorrhages, but no thrombi were detected.

Katz's (24) patient developed signs of cerebral hemorrhage and died the next day. The brain showed recent subarachnoid hemorrhage with hemorrhage into the left temporal lobe.

Sevitt's (25) patient died on the day neurological signs appeared. A large area of softening was found to involve the right occipital lobe, superior temporal lobe and internal capsule. No hemorrhage or embolus was seen. Microscopic examination showed a degenerated area infiltrated with "pus cells" near the cortical surface.

Cooke's (26) patient died suddenly from cerebral hemorrhage on the 13th day of heparin therapy. Extensive cerebral hemorrhage with previous emboli were found at postmortem. He concluded that this complication can occur without any therapy and that it may be difficult to prove statistically that there is any increased risk in the use of heparin. He considered, however, that the patient's death was directly due to heparin.

Miller's (27) patient had a slight hematemesis and bleeding from the gums on the third or fourth day of heparin treatment. On the tenth day she suddenly became unconscious and died two hours later. Some subarachnoid hemorrhage over the left cerebral hemisphere, extending to the base, the cisterna magnum and basilar cisterns, were found at necropsy. Several coronal sections showed a laminated clot, 5 cm. in diameter, occupying a smooth, firm space in the mid-portion of the left parietal lobe, adherent to the brain on its lateral aspect. The hemorrhage had ruptured into the left lateral ventricle and extended through the third and fourth ventricles to the basal cisterns. The general picture was not that of hemorrhage following the softening of infarction. There was evidence that a recent vegetation had been washed off the mitral valve. Miller concluded that the elevated venous clotting time had much to do with the cause of the cerebral accident. However, a contributory factor to this possibly was an embolus washed off from the mitral valve and locating itself in the cerebral artery. Added to this was a marked decrease of the coagulation time, which precipitated the hemorrhage.

Priest's (28) patient received dicoumarol, with a resulting prothrombin time of 200 seconds. On the third day of therapy cerebral symptoms were manifested, and death occurred soon after. A massive hemorrhage was found in the left cerebellar hemisphere. He concluded that fatal hemorrhage from the use of anticoagulants was suggested, although not proved.

Doane (29) reported a case in which the onset of neurological symptoms preceded death by one day. A massive and widespread infarction of the brain (multiple emboli), with a hemorrhage the size of a dollar in the right cerebellar hemisphere, were found at autopsy.

Levy and McKrill (30) described a patient with cerebral hemorrhage involving the left frontal and parietal lobes and originating from the left middle cerebral artery. He believed that heparinization favored fragmentation of the vegeta-

tions leading to embolism, and that large cerebral hemorrhages are due to bleeding into infarcted area as a result of diminished coagulability of the blood.

DISCUSSION

The foregoing observations have an important bearing on the course of events leading to so-called spontaneous massive cerebral hemorrhage in general. Globus (31, 32) has assembled anatomic and clinical observations to support the concept that a focal encephalomalacia precedes the terminal hemorrhagic event. A somewhat localized disease of the cerebral vessels results in the closure of some vessels in one or more circumscribed areas. This leads to the creation of an ischemic zone and a consequent focal encephalomalacia. With the production of such cerebral softening, an area of diminished resistance is created. In the presence of a diseased blood vessel and increased vascular tension, a reduction in the consistency of the surrounding tissue of the brain is an essential precursor to the rupture of the vessel wall and the unhindered escape of blood. The anatomic manifestations in support of this view are the presence of generalized vessel disease, the diffuse productive changes throughout such brains, the fairly well-defined organization in the wall limiting a hemorrhagic cavity, and the presence of exposed blood vessels in the hemorrhagic cavity.

The findings in cerebral hemorrhage following treatment of subacute bacterial endocarditis with anticoagulants tend to support this view. The terminal hemorrhage is usually preceded by clinical manifestations of a cerebral accident from several weeks to a few hours before death. When symptoms occur within a few hours before the patient succumbs, they are usually minimal at first and then precipitously increase. Postmortem findings generally give evidence of multiple embolic infarctions and an area of encephalomalacia into which bleeding occurred. In one case a recent vegetation was shown to have been washed off the mitral valve. Thus it would appear that a diseased valve throws off emboli to cerebral vessels causing one or more areas of infarction. This gives rise to neurological manifestations of a cerebral incident. Concurrently the therapeutic use of heparin and the reduced coagulability of the blood causes within a period of several hours or days further cerebral dysfunction. The initial symptoms, minimal at first, precipitously increase until terminus. There is continuous oozing of blood which cannot clot, into softened tissue, through a cerebral vessel injured by embolization. Autopsy discloses evidence of previous multiple embolic infarctions and an area of encephalomalacia into which bleeding has occurred; the blood remains fluid, showing little tendency to organize.

Bleeding into areas other than the brain has been reported in the literature. These are microscopic and gross hematuria, ecchymotic and purpuric areas over extremities, bleeding into elbow and knee joints, spontaneous epistaxis, hematemesis, and bleeding from operative wounds. Meyer (33), using dicoumarol, reported microscopic hematuria and occult blood in the stool. In one case, gross bleeding occurred when curettage of the uterus was performed at the time dicoumarol was being administered.

Wasserman and Stats (34) reported a series of cases that were treated with

dicoumarol. They noted a tendency to hemorrhage in any patient receiving dicoumarol in whom an unrelated lesion that might bleed was present. Examples of this included bleeding into the skin in a case of eczema, bleeding from the kidney in a patient with renal calculus, bleeding from ulcers of the extremities in thromboangiitis obliterans, and bleeding into the pleural cavity following pneumothorax in a case of pulmonary tuberculosis. Bleeding from operative wounds also tended to occur. In all these instances, bleeding occurred when the prothrombin was less than 20 per cent of normal.

Stats and Neuhoof (35) reported bleeding from the operative site in three patients receiving heparin (intramuscular aqueous solution). The medication was administered over a period of several months to most of the patients of a general surgical service. Hemorrhage into an internal organ was never observed.

The anticoagulant drugs show little tendency to cause hemorrhage except where there is preceding vascular injury. Areas that are susceptible to trauma are also the sites of predilection for bleeding during anticoagulant therapy, for example, nasal, gastric, and rectal mucosae, and joints.

There is some evidence, however, that hemorrhage can also occur in tissues containing intact blood vessels. The effect of heparin would be to increase the vascular permeability to the exudation of blood. The presence of metachromatic granules around the arteries would tend to support this view (9). In cases that have had splenectomies for thrombocytopenic purpura, there is a lapse of a few days before the platelet count is restored to normal. Nevertheless, the bleeding tendency is usually controlled shortly after ligation of the splenic vessels (38). Also, cases of thrombocytopenic purpura have had their bleeding tendency controlled by the administration of protamine, which neutralizes heparin (36).

On the other hand, according to Rigdon and Wilson (37) heparin itself has no effect on capillary permeability, and therefore in all likelihood is not the primary cause of cerebral hemorrhage in subacute bacterial endocarditis treated with heparin. They found that in the skin of rabbits treated with xylene, trypan blue dye localized in the inflamed areas and there was no difference either in time of appearance of the dye or in its quantity when heparin was given as compared to the controls which did not receive any heparin.

SUMMARY

1. The history of the development of heparin, its relation to mast cells, chemistry, mechanism of action, physiology and clinical application are summarized.
2. Two cases of cerebral hemorrhage in subacute bacterial endocarditis following the use of heparin are described.
3. A review of similar cases in the literature is presented. Conclusions reached were that a previous area of encephalomalacia produced by embolus from a vegetation on a diseased valve serves as an area of lowered resistance to the rupture of a cerebral vessel. The decreased coagulability of the circulating blood due to heparinization permits uncontrolled extravasation of blood through a ruptured vessel into the surrounding area of tissue softening, leading to massive

cerebral hemorrhage and death. A similar mechanism has been found to operate in cases of so-called spontaneous cerebral hemorrhage.

4. Some of the other hemorrhagic manifestations which are found in patients receiving anticoagulant therapy are noted.

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HUNGER AND APPETITE: SOME DEFINITIONS AND CONCEPTS*

HENRY D. JANOWITZ, M.D.**, AND M. I. GROSSMAN, PH.D., M.D.

Department of Clinical Science, University of Illinois, College of Medicine, Chicago, Illinois

Inexactness and confusion mark the present use of the terms hunger and appetite and related terms by physiologists and clinicians. Although it is recognized that the problems involved cannot be solved by definitions alone, it is intended in this paper to clarify somewhat these terms and concepts in the hope that exactness of definition will allow a more fruitful experimental approach. One further point should be noted here: the field of hunger and appetite does not suffer from lack of terms, and no new words need be invented. The effort will be rather to make more precise the definitions of the existing terms. No exhaustive review of the complex literature in this field is intended, and only papers dealing with the points at issue will be cited.

The dominant conception of hunger has been a mechanical one during the last twenty-five years. When Cannon (1) in 1912 showed that his student Washburne could recognize the periodic gastric contractions as an epigastric ache, hunger was reduced to the hunger pang. Although Carlson (2) in his classic work "The Control of Hunger in Health and Disease", started with the broader conception of hunger as a "biological condition which leads to the taking of food", the direction of his investigation resulted in the same reduction of this concept to the narrow one of the epigastric pain which he considered the "one indispensable element in hunger". For this school of workers hunger, synonymous with the epigastric pang, was the result of the periodic gastric "hunger" contractions, and these in turn were shown to be autonomous. As late as 1934 Cannon (3) vigorously defended his by then classic concept of hunger as essentially a problem of sensation and one of local sensation (that is, gastric sensation). It is interesting to note that thirst also was conceived by him as a problem of local, in this case pharyngeal, sensation.

The Incompleteness of the Gastric Contraction Concept. That such a narrow concept seems inadequate at present is the resultant of three main lines of investigation. First, experimental evidence has been accumulating which is difficult to harmonize with the gastric "hunger" contraction theory of hunger. The behavior of gastrectomized men and animals, the normal eating patterns of various species in which complete gastric denervation has been accomplished, the evidence that insulin increases and the sympathetic amines decrease food intake in the animal after such gastric denervation, all this is highly incompatible with the older concept. Second, the investigation by the physiologically minded psychologists of the concepts of bodily needs and the corresponding variations in food-taking behavior; and, third, the studies concerned with energy exchanges

* Submitted in partial fulfilment of the requirements for the degree of M.S. in Physiology of the University of Illinois.

** Welt Fellow in Medicine of the Mount Sinai Hospital, New York City.

in the animal bodily economy have emphasized the necessity for understanding the *regulatory* mechanism involved in hunger and appetite.

Historically, the necessity for considering some central regulatory mechanism is not new. Pavlov (31) had raised the question of a "food center", and Hoelzel (32) in Carlson's laboratory stressed central factors in hunger from evidence based on introspection that the periodic gastric contractions could occur without giving rise to hunger sensations.

Need for a Regulatory Conception. This is not the place to detail all the evidence, and, indeed, all the evidence is not yet available, but the overall features of a regulatory mechanism are obvious from the normal eating behavior of men and animals. The constancy with which bodily weight is usually preserved over long periods of adult life despite the wide variations of energy output is proof of a striking adjustment of food intake to some bodily needs. And the prompt clinical inference that disease is present when this constancy of bodily weight is disturbed is further illustration of this almost too obvious point. Indeed, the normal growth and development of the organism depends on its ingestion from the environment of the proper amounts of a wide range of substances: water, minerals, carbohydrates, fats and proteins, trace elements and vitamins.

The problem of hunger and appetite is an analysis of the factors involved in the adjustment of the intake of required nutritional materials to bodily needs. In this perspective hunger would seem logically best considered as an overall state and in terms of physiological needs and nutritional requirements. If the tendency of men and animals to seek out and ingest food in the attempt to adjust intake to bodily needs is considered in some overall pattern, this food seeking drive can be discussed in terms of three superimposed aspects:

1. The physiological aspects, which may range from biochemical determinants to homeostatic regulatory mechanisms,
2. Behavioral aspects,
3. Conscious aspects.

Analysis of the problem in terms of these three panels—physiological state, behavioral or activity level, and conscious or psychic aspects does not imply any dualistic or "trialistic" concept of the animal organism, but is simply an approach to some of the component parts of the total organic reaction. A holistic point of view is implicit in the present discussion.

The Hunger State. Based on the definition already proposed by Ivy (4), the following definition is suggested: *The hunger state is the physiological state resulting from the privation of food of a specific or general type and abolished by the ingestion of these foods.* This state is primitive, that is, unlearned and independent of conditioning. From the nutritional aspect deprivation of specific food substances leads to structural as well as functional changes, which may or may not be reversible. From the physiological point of view the states which result from privation may require varying lengths of time until the specific lack manifests itself, but they are reversible. If an attempt is made an operational definition of the hunger state it may be advisable to measure this simply in terms of the length of time the animal has been deprived of food, of either a specific

or general type, provided account is taken of food and water reserves. The hunger state may also be considered in terms of its manifestations, which are of two main varieties: (1) *hunger behavior* which can be observed in man and animals, and (2) *hunger sensation* which can be studied only in man.

Hunger behavior is the motor activity induced by the hunger state independent of learning. Decerebrate animals and anencephalic infants manifest a diffuse general restlessness and increased motor activity after deprivation of food. This heightened activity subsides after feeding. In the decerebrate pigeon, for example, placing noncaloric bulk in the crop resulted in a diminution of restlessness and pecking (5). The responses of decerebrate preparations to parenteral feeding and the results of denervating the gastrointestinal tract in these animals have not been studied. The newborn mammal offers a useful subject for further studies on hunger behavior, and some preliminary experiments indicate that the generalized restlessness will subside after a short latent period following feeding with various types of fluids, the period of subsidence being much longer with calorically significant feedings (11).

In normal animals the level of activity fluctuates with a variety of changes in intra-organic states; estrus as well as want of food in the rat is accompanied by high levels of activity, marked running for example. This aspect of hunger behavior lends itself to quantitative measurement, and the running activity of the rat has been rather carefully studied in this connection. It has been shown that rats maintained on an adequate dry diet and free access to water will markedly increase their running activity if deprived of food, or water, or both, and will sharply decrease this activity when permitted access to both (6). Deprivation of thiamin chloride (6), or the entire vitamin B complex (7) will also result in increased running, until the supervening polyneuritis interferes. Deprivation of magnesium, total inorganic ions (8) and Vitamin A (9) appear not to result in any such increased running activity.

With the growth of the organism this hunger behavior is suppressed and modified by cortical associations, although some elements of diffuse restlessness, such as the increased excitability of the knee jerk reflex, persist. Discussion of the role of this hunger behavior in the total food seeking and taking behavior of the animal is postponed until hunger sensations are considered, but it has been suggested that from a teleological point of view the increased running of the deprived rats functions both to increase the organisms chance of coming into contact with nourishment in the environment, and to remove the animal from its highly populated home areas with their food shortages (6).

Hunger sensations are the mental correlative (the psychic adjuncts) of the hunger state. These include the feeling of generalized weakness, fatigue, dizziness, irritability, nausea, headache, the sensations associated with sweating and trembling, feeling of emptiness, hollowness, epigastric tension, distress, pang, cramp and pain.

In studying sensations one is forced to rely on the verbal reports of trained human subjects. To interpret the cries of animals as meaningful expressions of sensations is a highly hazardous as well as inferential matter, and limits the use

of animal studies in this context. The hunger sensations are the reports of human subjects who have had experience in observing their own sensations, and as here defined they have long been known. Hippocrates (10) in his treatise *Ancient Medicine*, gave a vivid description of them. It is only recently that the other components of hunger sensations have been neglected in favor of the epigastric pang. Carlson (2) also recognized them and, grouping them as "some accessory phenomena of hunger," ascribed them all to changes caused reflexly by the hunger tonus and the hunger contractions of the empty stomach, although he admittedly had difficulty in subsuming "weakness fatigue" under this explanation.

Studies in this laboratory (11, 12) indicate that the extragastric sensations play the predominant role for many individuals in their complex of sensations. The hunger pangs are rare, even in people experiencing what they call normal hunger, under ordinary habits of eating. This, therefore, led to the conclusion that the epigastric pang is itself but one of the sensations in the sensation complex of hunger. The other hunger sensations can exist in its absence and indeed their quality is not detectably altered by its elimination.

Central versus Peripheral Origin of Hunger. One of the immediate advantages of this broader point of view of the hunger sensations is that it helps clarify the old problem of peripheral versus central origin of hunger. If one considers the sensations *per se*, then hunger sensations, like all other sensations, arise from stimuli acting on the brain, and theoretically these stimuli can be either of a reflex or humoral nature. Aside from the stimuli arising from the contraction of the stomach and upper gastrointestinal tract, recently shown (12) to be mediated by the thoracolumbar sympathetic system, the details of reflex stimulation are unknown (more is known about the pathways mediating anorexia). Of the humoral stimuli to the central nervous system little is known aside from the stimulating effect of insulin, an effect which is dependent upon the hypoglycemic action of this hormone. Spontaneous hunger, however, cannot be correlated with blood sugar levels; hypoglycemia seems to play only an emergency role in extreme situations. Furthermore, the site of stimulation by insulin-induced hypoglycemia, whether acting directly on the brain or through nervous or chemical effects arising in other tissues, is unknown. In this connection the actions of the sympathetic amines are interesting. Five milligrams of d-amphetamine will abolish in most individuals all their hunger sensations, will inhibit food intake in normal animals, and will inhibit sham feeding. The evidence of Harris, Ivy and Searle (13) that amphetamine depresses food intake in the gastric denervated animal, and some recent observations (11) that d-amphetamine abolishes hunger sensations in patients who have undergone vagotomy or sympathectomy and in patients with high spinal cord lesions, would point to a direct action of these drugs on the brain but the exact site of action is unknown. The absence of any effect of these drugs on taste thresholds and our failure to find any effect on olfactory acuity (11) is a bit of negative evidence in this problem.

Learning and the Hunger State. It should be stressed that the hunger be-

havior already discussed is an unconditioned, unlearned primitive response, and this may hold true for the hunger sensations, considered solely as the psychic concomitant of the hunger state in the intact individual. However, these hunger sensations have more than this "bare" significance, they acquire "meaning" for the organism through its experience. Thus, for example, the newborn mammal manifests restlessness and an inherited sucking reflex during the hunger state. This leads to the ingestion of milk, which induces repose. The frequent repetition of this cycle establishes a conditioned state in which the animal finally learns that the ingestion of food leads to abolition of the tensions accompanying the hunger state.

At this point in the growth of the organism, conditioned behavior is present superimposed upon and absorbing the unconditional unlearned aspects of reflex responses. This learned type of behavior in food seeking and food ingestion may be called for simplicity appetitive behavior. Some psychologists call this type of activity "goal directed". This appetitive behavior, since it intimately involves discriminative awareness, is influenced by conscious factors. In animal experimentation it is this which is usually measured in terms of the intake of available food matter, as rates of intake, volumes of intake, etc. And considered in such terms it is entirely satisfactory since it can be measured objectively and independently of associated conscious states. The experimental ease and advantage of such a procedure, however, should not alter the equally obvious fact that in man the conscious aspects are present, and can be ascertained by questioning. Although some investigators would prefer abandoning the term appetite, in man it seems to clearly represent the conscious aspects of appetitive behaviour. *Appetite is the desire to eat, and specific appetites are desires to eat specific foods.* This definition seems etymologically and physiologically sound.

The Relation of Desire to Need. The problem of appetitive behavior and appetite in man in its relationship to bodily needs is reflected in the extensive literature on self-selection of diet in infants and animals. Richter (14), one of the pioneers in this field, considered appetites as the direct expression of internal organic states of need, and maintained that self-selection, or correction of diet induced by various hormonal or fluid balance disturbances are part of an automatic, self-correcting, homeostatic mechanism, independent of experience. A critical review of this literature reveals wide variations in the range of the experimental animal's ability to adjust its intake to these disturbances; the animal may fail to make the correct choice or correct avoidance. The mechanisms of these responses are not entirely clear, but the animal's ability to learn is definitely involved (15). Young (16, 18), in a series of experiments on food preferences, began with the assumption that these preferences were due directly to partial hungers (Richter's appetite), and that they expressed variations in need. His results, however, led him to conclude that "the rat accepts some foods and rejects others, he develops food preferences which do not agree with his bodily needs, he forms dietary habits which tend to stabilize his selection of food". These food habits tended to form in agreement with palatability and only indirectly with need. Warkentin and Ivy (19) found that food preferences may

change suddenly without apparent cause. In another type of self-selection experiment, selection for maintenance, where a variety of purified nutrients are offered, the animal's ability to adjust food intake to needs has been demonstrated in an overall pattern; the rat, for instance, within limits, eats for calories (19). But the work of Scott (20) has shown how variable this response may be to a variety of purified substances of each of the major categories of foodstuffs and vitamins. Often no direct relationship between need and intake could be demonstrated and only simple or random preferences were displayed. Young has recently stated this in these terms: "Animals learn to select and to seek foods which they *like* rather than foods which they need (require nutritionally). To a considerable extent, however, animals like what they need" (21).

Conditioned and Unconditioned Food Taking Behavior. From the foregoing brief survey of the view of the major investigators in this field it will be readily recognized that the pivotal point about which the concepts of all of them turn is the question of how much or how little learning or conditioning contributes to food-taking behavior. On this question much can be gained by considering the point of view of modern physiological-psychologists toward all animal behavior irrespective of the old argument of "heredity versus environment". It is now recognized that both unlearned and learned behavior patterns contribute to animal behavior and that the two components are integrated, that is, the unlearned behavior serves as the framework on which the learned behavior develops. Marked individual variations in the patterns of learning occur within a given species. The differences between species are even greater. As the phylogenetic scale is ascended the patterns of behavior become less stereotyped and more dependent upon cortical functions (22). Food taking or appetitive behavior as outlined above can, thus, be profitably considered within some such framework. The unconditioned hunger state gives rise to hunger behavior and to hunger sensations. Under normal circumstances the ingestion of food suppresses these phenomena created by intraorganic states, and the tensions associated with them. The repetition of such cycles leads to the conditioned seeking for and ingestion of food or *appetitive behavior*, which is largely dependent on cortical function but presupposes the unlearned substrate.

Problems in regulation. Viewed in this perspective the relationship between appetitive behavior and bodily needs opens up fruitful areas for investigation, and these are being studied from many points of view at present: (a) conditions within the organism: changing energy requirements, physico-chemical variations, hormonal alterations, varying states of need; (b) patterns in the organism's feeding behavior: hoarding, persistence or abandonment of patterns under stresses; (c) variations in the nature of the available food: alteration in dilution and concentration of nutritive density; factors which may be considered under the general rubric of *acceptability* of given foods; variations in general environmental condition such as external temperature, studied carefully by Brobeck and his coworkers (23).

Clinical human material is sorely needed in these fields. For example, information on the salt intake of patients with cardiac decompensation, and

Addison's disease; the spontaneous intake of diabetic patients etc. should be investigated. Taste thresholds in human disease are not available.

Although all these studies vary the stresses upon the regulatory mechanism responsible for adjustment of need to intake, very little is known about this mechanism itself. What is already known indicates that it is capable of responding to *multiple stimuli*, which at the moment cannot be reduced to some single factor.

Some features such as the rates of ingestion of food (which in general are directly related to the amount of food still to be eaten), and the constancy of body weight cited above, point to considerable sensitivity and precision in the regulatory mechanisms. And, indeed, if an attempt is made to visualize some central device, it must depend, as Brobeck has pointed out (23) "upon some reversible change which occurs during assimilation, a change able to activate or to inhibit the sensitive cells".

However, in studies in this laboratory the parenteral administration of glucose and protein hydrolysates has not influenced oral food intake appreciably in two species in short term experiments (24, 25). These and reports by others on the responses to food deprivation in several species point to some sort of "inertia" in the regulatory systems involved. Other evidence, however, suggests that different factors are involved in the day-to-day or meal-to-meal adjustments from those involved in balancing intake to need over longer periods of time (11).

Regulation and satiety. There is considerable evidence that the ingestion of food satisfies more than energy—or even nutritional requirements. For example, the absorption of a meal carefully administered intragastrically has no inhibitory effect on real or sham feeding in the dog. This type of evidence indicates both that *appetitive behavior* may be completely dissociated from caloric requirement, and that there are "gustatory" needs which also must be satisfied. This situation is quite different from that occurring in sham drinking where placing water in the stomach will inhibit drinking after a suitable latent period (26, 27).

Since the intake of food is the resultant of forces ranging from the physiological to the environmental (conceived in its widest terms), it is apparent that the intake of food satisfies a diversity of the organism's desires and needs. The ingestion of a meal leads to the loss of the desire to eat, and to the temporary inhibition of further intake of food. It leads, that is, to the disappearance of appetite and the appetitive behavior. *This state of lack of desire to eat conceived as a total phenomenon is satiety or physiological anorexia.* This is clearly distinct from simply absorbing the required nutrients, or from the repletion of the hunger state. The evidence from intragastric and intravenous alimentation in both men and animals indicates that these procedures do not lead to satiety; similarly the ingestion of an acceptable meal leads to satiety before the repletion of the hunger state by its absorption can be accomplished; or a meal may lead to satiety although not nutritionally adequate. Satiety for food in general, or for a given food, can be conveniently measured by the animal's refusal to continue eating a given food, or foods. Alternately, Scott has suggested to us "The

measure of satiety, satiety value, of a food or meal is the sum or average of its contributions to the diverse satisfactions one may obtain from eating" (28).

Appetite and Satiety. Under normal circumstances the hunger state is associated with the desire to eat, which we have called appetite and, on the basis of the organism's past experience that ingestion of food abolishes the tensions of the hunger state, leads to the intake of available food. Its food preferences express this experience and mediate between intake and need. Likewise under normal circumstances the intake of food (appetitive behavior) leads to the inhibition of further eating, and to the disappearance of appetite in man (satiety).

Disturbances of Appetite. Under abnormal circumstances, however, there may occur dissociations between the hunger state and its corresponding appetite

TABLE I

BODILY STATE	ACTIVITY STATE	PSYCHIC STATE
Hunger (Depletion)	Hunger Activity ↓ Conditioning ↓ Appetitive Behavior	Hunger Sensations ↓ Conditioning ↓ Appetite
Repletion	Absence of Hunger Behavior and Appetitive Behavior	Satiety

This table should not be construed to indicate that the bodily state in the left column invariably invokes the activity and psychic states listed in the other columns. These inter-relations, not being stereotyped, form the subject matter of the physiological analysis of hunger and appetite.

and appetitive behavior; or between the satisfaction of need and satiety. These discrepancies between bodily needs and actual intake or desire for food can be classified into three main categories.

A. The hunger state may exist without the desire to eat or without the intake of food. The obvious example is the circumstance when the available food is unacceptable for a wide variety of reasons. Fever and liver disease represent pathological situations in which metabolic requirement may be increased with loss of the appropriate appetite. This example is by traditional usage called *anorexia*, or *hyporexia*, if partial. This definition is neutral in tone and does not imply loathing or disgust for food. While anorexia may be associated with these affective states, it is not necessarily related to them. In the experimental anorexia which occurs in intestinal obstruction the role of the vagus pathways has been demonstrated by Herrin and Meek (29). It might be added that ordinarily the hunger sensations and the desire to eat are so closely associated that any dissociation is extremely unusual. However, in some individuals the

hunger sensation may become so strong that nausea may be predominant and actually lead to loss of appetite.

B. Appetite may exist and food be ingested in the absence of the need, or food may be ingested in excess of the metabolic need. This is *hyperorexia*. The overeating of animals with hypothalamic lesions, frontal lobe lesions in man, "neurotic eating" and some stages of exogenous obesity seem to fit in here. "The foundering of cattle and horses when offered an excess of highly palatable food" has also been suggested (28) as an example of *hyperorexia*.

C. Unusual materials may be ingested without relation to bodily needs. Such perverted appetite and intake have been classified as *parorexia* (30). In analyzing such *parorexia*, it should be considered that some unusual materials may have a relation to bodily needs.

These varieties of defective, excessive and perverted appetite thus can be considered within the framework of disturbances of regulatory mechanisms of hunger and appetite, and this theoretical scheme directs attention to the multiple nature of the factors involved in normal food behavior. See Table I.

SUMMARY

The study of hunger and appetite is concerned with the regulation of the intake of food in accordance with bodily need. *Hunger*, the bodily state arising from deprivation of food, manifests itself in the form of *hunger behavior* and *hunger sensations*. With learning or conditioning the animal or man comes to recognize the association between ingestion of food and subsidence of hunger sensations and behavior so that the hunger sensations then give rise to the desire to eat, *appetite*, and the hunger behavior becomes incorporated in the learned activity which we call *appetitive behavior*. Ingestion of food leads to inhibition of the appetitive behavior and is accompanied by a loss of the desire to eat, *satiety* or *physiologic anorexia*, and under pathological conditions this association between the hunger state (need) and desire for food (appetite) is disturbed in the direction of excessive, defective or perverted tendencies.

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COINCIDENTAL POLYPI, DIVERTICULITIS AND MULTIPLE CARCINOMA OF THE COLON¹

SAMUEL H. KLEIN, M.D.

It is well known that the clinical differentiation between the hyperplastic stenosing type of diverticulitis and carcinoma of the colon is often difficult if not at times impossible. Not infrequently, too, the surgeon at the operating table is unable to determine with certainty whether he is dealing with diverticulitis or carcinoma so that the diagnosis must await the report of microscopic examination. Both conditions may produce a palpable, tender, abdominal mass, obstruction of the bowel lumen, fever, abdominal pain and diarrhea or constipation. Also, the roentgen appearance on barium enema examination at times may be inconclusive. While colonic carcinoma usually exhibits ulceration and a positive test for occult blood in the stool, diverticulitis with ulceration may also produce similar findings. The development of a pericolonic inflammatory mass, occasionally associated with perforation, abscess formation, and/or fistulization into an adjacent hollow viscus such as the small bowel, bladder or vagina may be still another feature common to both lesions.

It is generally believed that, in many cases, adenocarcinoma of the large bowel may originate in a pre-existing benign adenomatous polyp. Since these polypi are often multiple, it is not surprising that not infrequently one encounters two or more coexisting malignant neoplasms of the colon, or in some instances, the subsequent development of one or more colonic carcinomata in the same patient.

Diverticulosis may occur in any portion of the colon, in multiple foci or localized; however, in the majority of cases, the left side of the colon is particularly involved. By the same token, the complications of diverticular inflammation namely, perforation, inflammatory hyperplasia and fistulization are observed much more frequently in the sigmoid segment.

It is very questionable whether carcinoma may develop on the basis of a chronic diverticulitis. Also very infrequent is the concomitant occurrence of hyperplastic diverticulitis in one part of the colon and carcinoma in another.

The following case presents several features of unusual clinical and pathological interest.

CASE REPORT

History: The patient (L. E., Hospital #479018), a woman, aged 49 years, was admitted to The Mount Sinai Hospital from the Consultation Service on September 12, 1941. Her symptoms began in December 1940, consisting of constant, aching, abdominal pain. Her bowels were regular and the stools appeared grossly normal. After about two months, the pain became intermittent, severe and lancinating in character, and was associated with nausea and vomiting. In mid-August of 1941, the patient experienced violently severe cramp-like lower abdominal pain and diarrhea. She stated that she had lost forty-four pounds since the onset of her illness. Her familial and personal histories were irrelevant.

¹ From the Surgical Service of Dr. John H. Garlock, The Mount Sinai Hospital, New York.

Examination: Two tender masses in the abdomen were present: one, about 3.5 cm. in diameter, was situated beneath the right costal margin, the other a little smaller, in the right lower quadrant could also be palpated on pelvic examination in the right vaginal fornix.

Laboratory data: Blood count: hemoglobin 70 per cent; red blood cells 4,300,000 per cubic mm.; color index 0.8; white blood cells 16,600 per cubic mm. of which 61 per cent were segmented polymorphonuclear leucocytes, 17 per cent staff forms, 15 per cent lymphocytes, 1 per cent eosinophiles, 4 per cent monocytes and 2 per cent juvenile forms. Her temperature varied between 98, 100 and 102°F. The erythrocytic sedimentation rate was rapid, 18 mm. in 20 minutes. The blood Kahn test was negative. The urine was essentially negative. The stool, after three days of meat-free diet, was strongly positive to the guaiac test for occult blood. The Rehfuess test meal found normal gastric secretion. The blood pressure was 124 systolic, 68 diastolic. The electrocardiogram showed left axis deviation. Gastro-duodenal fluoroscopic visualization revealed no abnormality.

Roentgenographic examination of the colon after barium enema disclosed a stenosing lesion in the mid-transverse colon approximately 3.5 cm. in length, past which the barium could be introduced only with considerable difficulty. The proximal transverse colon showed marked irritability, spasm, deformity and numerous diverticula. It was thought that there was a diverticulitis of the hepatic flexure and proximal transverse colon, and that the lesion in the mid-transverse colon had the roentgen appearance of a neoplasm. However, in view of the presence of the inflammatory disease adjacent to it, the possibility of a diverticulitis in this section was also considered.

Course: After suitable preparation of the patient, operation was performed on September 17th (Dr. Garlock). The abdominal cavity was entered thru a right rectus muscle-splitting incision. The liver was found to be negative on palpation. There was a fist-sized mass involving the cecum and extending retroperitoneally, with adherence of the terminal loop of ileum and another more proximal small bowel loop. A second, somewhat smaller hard mass was also present, situated in the transverse colon near the splenic flexure and occupying almost the entire circumference of the bowel. The proximal adherent ileal loop was dissected free from the cecal mass, the terminal ileum transected about 30 cm. proximal to the ileocecal junction, both cut ends closed in layers by inverting sutures and isoperistaltic side-to-side ileosigmoidostomy performed.

The second stage of the operation was done on October 6th. This procedure consisted of resection of the terminal ileum, right colon, transverse colon, splenic flexure and the proximal portion of the descending colon.

Gross pathological examination of the resected specimen revealed the following: There was a neoplastic mass, 7 cm. in diameter, in the distal portion of the transverse colon; seven polypi situated between the ileocecal valve and the tumor, each measuring from 1 to 2 cm. in diameter; diverticulosis and diverticulitis in the cecum and ascending colon, with perforation of one diverticulum near the ileocecal valve producing a peri-cecal inflammatory mass with a central abscess cavity about 2.5 cm. in diameter. There was another polyp present distal to the tumor of the transverse colon. Several enlarged lymph nodes were noted in the pericolic fat tissue.

Microscopic pathological examination was reported as finding "infiltrating adenocarcinoma of the transverse colon; no metastatically involved lymph nodes; adenomatous polypi, one with focal de-differentiation; multiple diverticuli and acute diverticulitis of the cecum with pericolic abscess."

The postoperative course was satisfactory and the patient was discharged from the hospital on the 18th day in good condition. She remained well until 1946, when she again began to have intermittent attacks of colicky pain in the lower abdomen and in the back. On April 30, 1948 she was suddenly seized with very severe pain in the left lower quadrant of the abdomen and in the periumbilical area. The pain was constant and the patient vomited repeatedly. She was re-admitted to the hospital on the following day, about 18 hours after the onset of the acute symptoms, suffering obviously from acute diffuse peritonitis. She

appeared acutely ill, was dehydrated, mentally disoriented, restless, and uncooperative. Her temperature was 103 degrees Fahrenheit, the pulse 88 per minute, the blood pressure 108 systolic, 68 diastolic. The abdomen was distended, exquisitely tender throughout, with diffuse muscle spasm and rebound tenderness. Scout X-ray film of the abdomen taken on admission revealed no free air beneath the diaphragm and no evidence of small bowel dilatation. The leucocyte count was 14,750 per cubic mm., with 76 per cent polymorphonuclear leucocytes, 12 per cent lymphocytes, 8 per cent basophiles and 4 per cent monocytes.

Since the peritonitis was diffuse and already of 18 hours duration, a conservative course of therapy was decided upon in the hope that localization would occur and the apparently perforated intestinal lesion become sealed off. Consequently the patient was supported with intravenous infusions and blood transfusions, and streptomycin and penicillin were administered. Under this regime, although her temperature remained elevated between 102 and 103°F., her general and mental condition improved, the diffuse peritoneal signs subsided after a few days, and a large, firm, tender mass developed in the left side of the abdomen reaching to the right as far as the right rectus scar of the previous operations.

By March 12th, there was redness of the skin at the lower angle of this scar, with underlying fluctuation in the mass at this point. Under general anesthesia, an incision was made in this area, permitting the escape of several ounces of very foul pus. Examination of the abscess cavity revealed a tract which extended deeply into the abdominal cavity; this, however, was not explored further at this time, and the abscess cavity was packed widely open with gauze. Culture of the pus grew out *B. Coli* and enterococcus. The patient then proceeded to improve rapidly, her fever subsided, the large mass in the left side of the abdomen became smaller, and she was discharged from the hospital on April 13th. At this time the sinus at the lower angle of the right rectus scar was still draining a small amount of pus, and the residual mass was slightly tender. She was then observed at intervals in the Follow-Up Clinic; the sinus closed after several weeks, but the tender mass persisted. Because of the previous episode of free perforation and the apparent persistence of inflammatory activity in what was considered to be probably a sigmoidal diverticulitis, barium enema roentgen examination was deferred for fear of initiating another perforation.

However, on September 6th, it became necessary to re-admit the patient to the hospital because she had begun to run low grade fever and had lost 10 pounds in weight. At this time, the still tender mass measured about 5 cm. in diameter, and the stool was faintly positive to the guaiac test for occult blood. Barium enema X-ray examination was attempted but was unsatisfactory because the patient suffered severe pain and tenderness. The pain and fever subsided under sulfadiazine chemotherapy and she was allowed to leave the hospital on September 22nd. A successful roentgen examination was finally obtained on October 26th. There was complete obstruction to the flow of barium at the mid-descending colon (the distal point of resection at the previous operation), and at this site there was a large, round, soft-tissue mass 7 cm. in diameter, a lobulated portion of which intruded into the lumen of the bowel. The appearance was most suggestive of a malignant colonic neoplasm which was thought to be primary in this area.

The patient was re-admitted to the hospital on November 6th. After routine preparation, she was operated upon on November 12th (Dr. Klein). The pre-operative clinical impression was that the firm, tender mass in the left side of the abdomen, which at this time extended upward toward the left upper quadrant, represented either an inflammatory mass secondary to perforation of a diverticulitis or of a second, primary neoplasm of the descending or sigmoid colon. The abdominal cavity was entered through a left rectus muscle-splitting incision. Palpation of the liver was negative. There was a large, hard mass in the left side of the abdomen, about 7 cm. in diameter, densely adherent to the peritoneum of the abdominal wall anteriorly and laterally; the peritoneum in these areas was markedly thickened. The mass was mobilized in front by incising widely the involved peritoneum from the abdominal wall and behind by freeing it from the kidney, ureter and posterior parietes. It was then found to consist of a large neoplasm of the stump of the descending colon to which had become adherent a loop of small bowel, both surrounded by much inflam-

matory reaction. Further dissection revealed the presence of a fistulous communication between the lumen of the adherent small bowel loop and that of the descending colon through the tumor. The previous ilcosigmoidal anastomosis was found to be situated about 15 cm. below the tumor mass; thus, adequate resection of the descending colon and upper sigmoid could be done without compromising the anastomosis. Just distal to the neoplasm a polyp 1.5 cm. in diameter was seen, attached by a narrow pedicle about 6 cm. in length. There was no gross evidence of diverticulosis. Wide resection of the descending colon stump and upper sigmoid was then performed, together with the involved small bowel loop. The cut end of the colon was closed in layers by inverting sutures, and end-to-end suture anastomosis of the ileum performed. The large raw area left after removal of the colonic segment and surrounding inflammatory tissue was drained through a left lateral stab incision.

The patient's convalescence was complicated by a wound infection, but was otherwise satisfactory. The wound healed slowly and she was discharged from the hospital on the 41st day in good condition.

Pathological examination of the resected specimen was reported as follows: "Blind segment of colon showing infiltrating adenocarcinoma and adenomatous polypi. Extension of carcinoma with fistulous tracts into segment of small bowel. Enlarged lymph nodes found in the pericolic fat tissue, but none showed metastatic involvement."

SUMMARY

The colon in the patient herein described was the seat of multiple, diffusely distributed adenomatous polypi and of diverticulosis localized to the right side. Inflammation and perforation of one of the diverticuli in the cecum produced a pericecal abscess and inflammatory mass. It is assumed that at about the same time, a benign adenomatous polyp in the transverse colon underwent malignant degeneration to form an adenocarcinoma. Several years following resection of the right side of the colon to the level of the mid-descending colon, there developed a second adenocarcinoma, this time in the descending colon, perhaps again in a pre-existing polyp. Clinically, however, in view of the previous occurrence of perforated hyperplastic diverticulitis in the cecum, it was natural to assume that this lesion was a perforated diverticulitis, although the possibility of its being neoplastic was also borne in mind. We were therefore faced with the difficult problem of the differential diagnosis between carcinoma and diverticulitis. Roentgen examination was of necessity delayed because of the persistent inflammatory activity of the mass in the left side of the abdomen which remained after the localization and subsidence of the acute, diffuse peritonitis, and the fear of inducing a fresh perforation. Of further interest is the apparent low grade of malignancy of both colonic carcinomata in this patient. In neither instance did the liver and regional lymph nodes present any evidence of metastatic involvement. This is particularly noteworthy in view of the long duration of the second tumor prior to its surgical extirpation, by which time local involvement and fistulization into an adjacent loop of small bowel occurred.

NONPARASITIC CYSTS OF THE SPLEEN

A REPORT OF TWO CASES

IRVING H. PARNES, M.D.

(Resident on the Surgical Service of Dr. J. H. Garlock, Mount Sinai Hospital, New York, N. Y.)

A review of the literature disclosed that up to March 1949, there were recorded 167 cases of nonparasitic cyst of the spleen. These have been divided into true and false cysts, the former being lined with a secreting membrane. Approximately 21 per cent of splenic cysts fall into the first group (4, 5). Parker and Brown (12) find that 10 per cent of their group of 164 collected cases are epidermoid cysts.

The pathogenesis of cyst formation in the spleen is still not fully understood. Among the etiologic factors considered are: congenital rests; trauma; infarction or hemorrhage associated with congestion of spleen during menstruation or pregnancy; and embolism or thrombosis of the splenic vessels. Two thirds of the reported cysts have occurred in women, and the great majority of these during the child-bearing age (1, 2, 7, 10, 13).

The symptomatology is usually rather meager. The patient may complain of vague dragging sensations in the upper abdomen and may have pain referable to the epigastrium and the left upper quadrant (15). Some patients have noticed a large, usually non-tender, mass in the left upper abdomen.

Examination has commonly revealed a large mass on palpation in the left upper quadrant extending beneath the left costal margin and pushing it outward; this localization differentiates a splenic cyst from one pancreatic or ovarian in origin.

Roentgenological examination shows a typical displacement of the stomach and the lower one third of the esophagus to the right, displacement of the splenic flexure downward, depression of the upper calyx of the left kidney, elevation of the left leaf of the diaphragm, and spreading of the lower left rib interspaces.

The treatment of cysts of the spleen is surgical. In the majority of instances this type of tumor mass has not been diagnosed preoperatively. When laparotomy reveals a large cyst of the spleen, splenectomy is indicated. Marsupialization is considered obsolete, as well as puncture of the cyst and coagulation of its contents (15). Local excision or enucleation of the cyst is no longer considered advisable.

The two cases herein reported show the transition of operative procedure from the conventional left rectus muscle splitting incision with a T extension to the combined abdominothoracic incision (3, 6).

CASE REPORTS

Case #1. History: Miss S. S. (MSH #541978) aged 22½ years, entered the Mount Sinai Hospital on November 19, 1945, with the complaint of left upper quadrant pain of four months' duration. She had had infectious mononucleosis 11 months prior to her admission to the hospital. After a three month convalescence she returned to her normal

activity. About four months later she began to have episodes of dull pain with sharp accentuation on deep breathing. This increased in severity with the pain radiating to the left shoulder.

Examination: The patient was a plump well developed young woman. Palpation revealed a large firm mass, slightly tender, in left upper quadrant, extending toward left loin. This was under the left subcostal margin and extended inferiorly. Blood pressure, temperature and pulse were within normal limits.

Laboratory Data: Hemoglobin, 70%; white cells, 10,200, with a normal differential; Platelets, 420,000. Hetrophile antigen titer was 1:32, normal. Urine was normal. Blood Wassermann test was negative, and blood chemistry was normal in all phases.

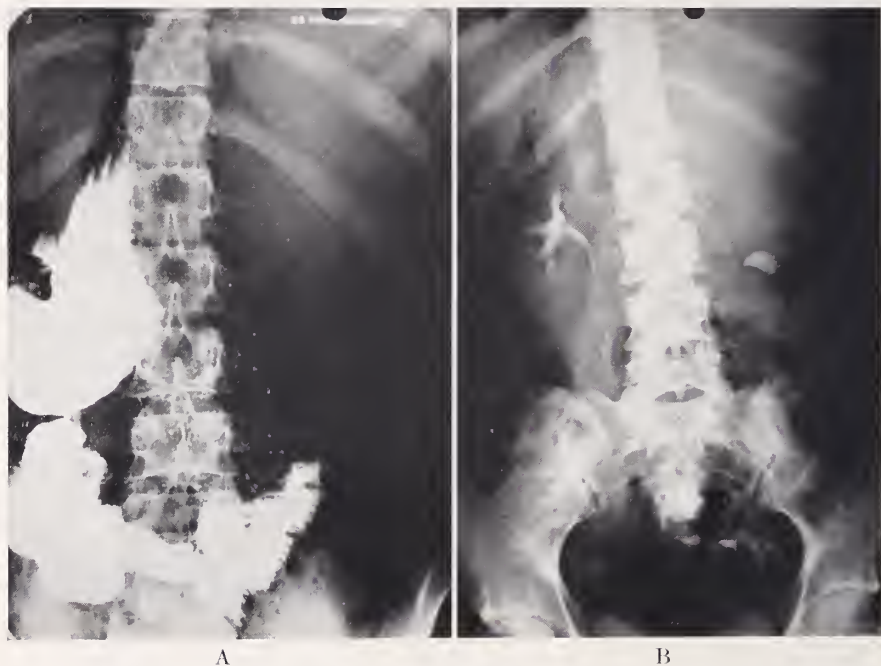


FIG. 1,A (Case #1) large mass in the left upper quadrant (spleen) displacing the stomach to the right and the small bowel downward.

FIG. 1,B (Case #1) The left kidney is displaced downward by the large extra renal mass in the left upper quadrant. There is evidence of extrinsic pressure on the superior and middle calyx on this side.

X-ray Studies: The chest film showed considerable elevation of the left leaf of the diaphragm. In gastro-intestinal films it was noted that the left upper quadrant mass did not arise from stomach, duodenum or large bowel. All of these structures, however, were displaced by the mass which was situated laterally and posteriorly (fig. 1A). There was linear calcification within the lower border of the mass. After intravenous urography it was thought that the mass was probably extrarenal, although the left kidney was displaced downward and the left renal pelvis was depressed (fig. 1B).

Operation was performed on December 4, 1945 under cyclopropane and ether anesthesia. A long left rectus incision was made revealing a large spleen measuring approximately 20 cm. in its largest diameter. Its shape was deformed by the presence of a large cystic mass contained within the spleen and bulging on both the upper and the hilar surface of the organ where the splenic tissue was reduced to a thin tense fibrous capsule. The enlarged spleen extended from the dome of the diaphragm down to the umbilical line. The liver was nor-

mal. A left T extension was made in the posterior rectus sheath. Despite this extension, difficulty in exposure was encountered. The spleen was mobilized and removed intact, following separate ligation of the vein and artery at the pedicle. Two Penrose drains were placed down to the large cavity in the left upper quadrant and the wound was repaired with buried figure of eight steel wire sutures.

The early post-operative course was quite stormy, marked by fever and by a psychotic episode that necessitated her transfer to a psychiatric hospital for a period of two days. On



FIG. 2 (*Case #1*) The gross appearance of the cyst of the spleen on sagittal section, showing the coarsely trabeculated wall and the thin rim of splenic tissue. Microscopic section of the cyst wall showed squamous cell epithelium.

return to the Mount Sinai Hospital her temperature continued to be elevated, finally reaching 104°F. An exploratory laparotomy through a small left oblique subcostal incision was carried out 42 days after first operation (Jan. 15, 1946). It revealed no evidence of infection.

The patient's condition continued to be poor and on January 19, 1946 (4 days after the exploration) bloody pleural fluid was aspirated from the right chest, and an X-ray examination following this suggested the probability of a pulmonary infarction. No evidence of phlebitis in the lower extremities was found. In another 4 days (January 23, 1946) 50 days following the original splenectomy, and eight days following the exploratory operation patient suddenly became dyspneic and died.

Pathological report of the surgical specimen was a "Very large epidermoid cyst of the spleen." (fig. 2).

The general autopsy revealed: "Multiple pulmonary artery emboli, infarction of both lower lobes of lung, the cause of death being pulmonary emboli."

Comment: The attack of infectious mononucleosis with attendant splenomegaly 11 months before admission may have been the basis for subsequent development of the cyst. It is known that infectious mononucleosis will cause enlargement and friability of the spleen (14). It is also well known that after splenectomy there is usually a marked rise in the platelet count which is more persistent than in other post-operative thrombocytoses. This increase usually appears after the first week (9, 16). A platelet count was not done post-operatively, and this might have suggested the use of heparin or dicumarol, even before there was evidence of pulmonary infarction.

Case #2. History: Mrs. D. K. (MSH #590623) aged 24 years entered the Mount Sinai Hospital on Jan. 8, 1949, complaining of the presence of a mass in the upper abdomen for past several months. She was well until six months before admission when she was suddenly seized with severe abdominal pain and a moderate rise in temperature. She first entered another Hospital for observation and left it without a diagnosis. Her private physician observing a gradual increase in the size of the abdomen diagnosed it as a cyst of the spleen and advised operation. There was no change in bowel habits and her appetite continued to be good. Her only symptom referable to the mass was a sensation of "something in the abdomen". The patient had one child two years of age.

Examination: The young woman was well nourished and apparently in good health. Her blood pressure and pulse were normal. There was a mass in the left upper quadrant, extending under the left subcostal margin. On palpation it was slightly tender, firm, non-mobile, suggestively cystic, occupying the entire left upper quadrant, extending across the midline and under the costal margin.

X-ray Studies: Gastro-intestinal films showed displacement of the stomach downward and to the right and displacement of the splenic flexure of the colon downward (fig. 3). Intravenous urography disclosed a large mass in the left upper quadrant, compatible with a tumor in the upper pole of the left kidney.

Operation: This was done under ether-nitrous oxide and oxygen endotracheal anesthesia. The patient was inclined on the table in left lateral position. The abdomen was opened through a small left upper mid-rectus muscle splitting incision. A cystic mass approximately 25 cm. by 15 cm. contained within the deformed spleen was found. Inasmuch as the mass and spleen were large and extended well under the left subcostal region it was felt that the best exposure would be obtained with a transthoracic extension. Therefore, the skin incision was extended from the upper angle of the rectus incision along the left eighth interspace, dividing the costal arch. The pleural cavity was entered, diaphragm incised radially, and a rib spreader inserted. This gave a good view of the spleen and its pedicle. The tumor mass was easily delivered into the wound, its peritoneal vascular attachments clamped and cut, the tail of the pancreas wiped off the tumor, and the splenic vessels individually ligated. One Penrose drain was inserted down to the splenic bed and led out through a lateral stab incision. The chest was closed in layers with interrupted silk, after expansion of the lung. The diaphragm was closed with interrupted silk. The abdomen was closed with buried figure of eight steel wire. No drainage of the chest. Patient received 1000 cc. of blood during the operation.

The post-operative course was uneventful. The patient was out of bed on the 1st post-operative day. The wound healed well and the patient left the hospital 12 days after the operation free of complaints.

The pathological report: "Huge cyst of spleen, probably traumatic in origin. Cyst lined by fibrous tissue. The remaining rim of splenic structure without significant changes." (fig. 4).



FIG. 3 (*Case #2*) Large mass in left upper quadrant displacing the stomach to the right and the transverse colon downward (combination barium enema and barium meal examination).

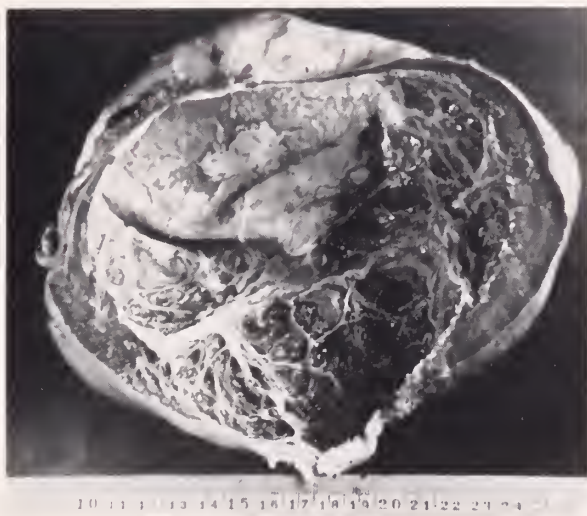


FIG. 4 (*Case #2*) Gross appearance of the cyst of the spleen on sagittal section.

Comment: This patient's illness seems to have begun as an acute episode six months prior to her entrance to the hospital. Her physician felt that patient had a partial splenic rupture, and watched the mass enlarge. The x-rays in this case also pointed to an enlarged spleen.

This tumor mass was larger than the previous one and it was felt that left costal margin could be entirely eliminated as a barrier by the abdominothoracic approach. The operation was greatly simplified by the exposure that this incision gave. The post-operative course was uneventful, and the patient has remained well (last seen March 13, 1949). It is felt that this incision is the approach of choice in intrabdominal tumors of this type.

This case is one which falls into the category of false cysts of the spleen probably traumatic in origin. It is in contrast to the first case in which there was found an epidermoid cyst with a true epithelial lining.

SUMMARY

Two cases of cyst of the spleen; one epidermoid in character, the other a false cyst traumatic in origin. Both were in young women, aged 22 and 24 years. One patient had completed a normal pregnancy 18 months before the onset of symptoms, which were ushered in by acute abdominal pain most probably due to a partial rupture of the spleen. The other patient had had infectious mononucleosis 7 months before onset of the recent symptoms, which consisted of dull and sharp pains in left upper abdomen. The first patient had a splenectomy through a left rectus muscle splitting incision with a T extension, and the second a splenectomy through a combined abdominothoracic incision.

It is felt that despite the larger size of the splenic cyst in Case 2 splenectomy was carried out with greater simplicity by reason of the abdominothoracic incision employed.

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MENIÈRE'S SYNDROME RELIEVED BY ELECTROCOAGULATION OF THE MEMBRANOUS LABYRINTH

REPORT OF CASE¹

JOSEPH G. DRUSS, M.D.

It is only within the last decade that the pathological condition likely to be responsible for the manifestations of Menière's syndrome became better understood. Hallpike and Cairns (1) were first to offer histological observations suggesting that a dilatation of the membranous labyrinth is the probable cause of this syndrome. They were corroborated by Altmann and Fowler (2) and by Lindsay (3). The manner in which the ectasia of the membranous labyrinth is produced, whether by an over secretion of endolymph, a disturbance in resorption, or possibly by abnormal biochemical changes in the fluid has not been definitely established. Nevertheless, it was quite natural, that in a surgical approach to the treatment of Menière's disease that was to follow, attention was to be directed to the affected site of the disturbance in the labyrinth and away from the eighth nerve. Previously the latter had always been the sole target for attack. Thus there was accordingly introduced a variety of surgical methods by a number of surgeons, Putnam (4), Berggren (5), Mollison (6), Cawthorne (7), Day (8), Goodyear (9), Wright (10), all of which entailed the destruction of the membranous labyrinth. Lampert (11), recently described an operation in which he was able to effect degeneration of the endolymphatic labyrinth by decompressing both the vestibular and cochlear parts of the membranous labyrinth.

The operative procedure employed in the case herein reported is a modification of the technic used by Day (8), in which he passes a fine needle through a window made in the lateral semicircular canal and coagulates the membranous labyrinth. With this procedure Day has succeeded in obtaining satisfactory and uniform results in a series of over 21 cases.

Despite obvious success in the treatment of Menière's syndrome the impression must not be gained that this surgical approach is recommended for all patients with aural vertigo. On the contrary, it is indicated only in that small group of cases which fail to respond to all forms of therapy such as sedation, nicotinic acid and other vitamins, intravenous injections of magnesium sulphate, and the administration of histamine. In evaluating any form of therapy for this condition, it must be borne in mind that the vertiginous attacks normally have a tendency towards spontaneous remissions.

CASE REPORT

History: M. K., a man, aged 56 years, was admitted to Mount Sinai Hospital on December 20, 1946. He experienced his first attack of vertigo impaired hearing and tinnitus in the right ear 10 years previously. Subsequent attacks occurred at about monthly intervals but more recently as often as 2 to 3 times a week. They were often associated with vomiting and occasionally with a strong desire to defecate. At times the vertigo was so

¹ From the Otolaryngological Service, The Mount Sinai Hospital, New York.

pronounced that he would fall precipitately to the floor injuring himself. The deafness began in the right ear, became progressively worse, and subsequently involved the left ear. The tinnitus was described as a buzzing sound in the right ear, and a high pitched sound resembling a steam whistle in the left ear. It often persisted in both ears between attacks.

Two years after the onset of the symptoms, the patient was admitted to the Neurological Institute where a diagnosis of Meniere's syndrome was made. He was discharged on a Furstenberg regime (salt free diet with limited fluids, supplemented by ammonium chloride), and was completely free from attacks for five years. Then, in spite of his steadfast adherence to this diet, they again recurred. Niacin and other vitamins were tried but without giving him relief.

Two months prior to his admission to The Mount Sinai Hospital the patient was investigated in the Consultation Service where the only significant finding recorded was a pronounced hearing impairment in both ears; the vestibular nerves responded normally to caloric stimulation at that time. He was admitted to the neurological service for possible section of the eighth nerve.

Examination: The patient held his head somewhat stiffly as though guarding against unnecessary movement and tilted to the right. Both tympanic membranes were normal. Tuning fork tests and audiograms revealed almost total loss of hearing in the right ear and a pronounced nerve type of hearing impairment in the left. There were spontaneous nystagmoid movements of the eyes (lasting for a few seconds) on extreme left lateral gaze. Caloric tests now elicited markedly diminished vestibular responses on both sides. Lumbar puncture gave clear, colorless fluid with an initial pressure of 100 which rose to 240 mm. of water after straining; cell count and Pandy test were normal.

Course: It was suggested by the otolaryngologic service that this would be a suitable case for destruction of the right membranous labyrinth and with the approval of the neurologic service this procedure was soon carried out.

Operative Procedure: Under gas and oxygen anesthesia, the typical Lempert endaural nov-ovalis fenestration was first performed in the usual way as a preliminary step. Following this, a fine angulated hypodermic needle attached to a Luer syringe was inserted into the fenestra, perforating the membranous labyrinth and directed toward the anterior and medial aspect of the vestibule (thus avoiding as far as possible the fallopian canal). A coagulating current from a Bovie apparatus with a dial setting at 35 was then applied to the needle for about a second and after a momentary pause again repeated. This was followed by an injection of 95% ethyl alcohol directly into the labyrinth. The tympano meatal flap previously prepared was placed over the fenestra and the wound dressed in the usual way.

The *post operative* course was most satisfactory. On the day following the operation the patient was able to take nourishment by mouth. There was a pronounced nystagmus to the left which persisted for about 2 weeks. The vertigo was considerably improved. A slight peripheral facial paresis in the right was present, but cleared up entirely within 3 weeks. He was permitted out of bed on the 12th day—his gait was unimpaired and the vertigo was not made worse on walking. The patient stated that the buzzing in the right ear had become much less pronounced.

He was discharged 3 weeks post operatively and was subsequently followed up in the out patient department. The operated endaural cavity healed completely and was lined throughout by epithelium. Repeated examinations, the last one made on October 27th, 1948 consistently disclosed a total loss of function of the right cochlear nerve and a total loss of responses to caloric stimulation of the right vestibular nerve; the left vestibular nerve gave normal but diminished responses, and there was no spontaneous nystagmus. Repeated audiograms showed little or no improvement in the hearing of the unoperated left ear. With the use of a hearing aid, however, the patient could hear loud spoken words. He gets around very satisfactorily and has had no attacks of vertigo since the operation.

Comment: This patient had been suffering from periodic attacks of vertigo increasing in intensity for 10 years and totally disabled him at the time of his last

admission to the hospital. Conservative measures having failed within the last five years to afford relief, operative intervention was decided upon. A relatively new procedure designed to destroy the contents of the labyrinth was carried out in this case. A fenestration operation was followed by the application of a coagulating current to the labyrinth and by an injection of alcohol into the cavity. Either one of the two last destructive measures alone usually suffices to produce a total loss of vestibular function. Unfortunately, with the operative technics employed thus far not only is the vestibular function lost but the hearing also is usually destroyed. Histological studies of the labyrinth in monkeys in which this organ was destroyed by coagulation were recently made by Schall and Rambo (12) which would seem to corroborate the observation that the hearing and vestibular function are both destroyed. The ideal procedure naturally would be one which is effective in relieving the vertigo and tinnitus without destroying the residual hearing. Since the patient herein reported was almost totally deaf in the operative ear and with little hopes for improvement, the fear of damaging the cochlea during the operation was no problem; consequently to be reassured of completely destroying the labyrinth both the coagulating current and the alcohol injection were used. The patient obtained almost immediate relief of symptoms. This is not an unusual observation, although in some of the cases reported, there was a lapse of months following the operation before the unoperated labyrinth adjusted itself. Up to the time of his last follow up examination, approximately 2 years post operative, the patient has been free of vertiginous attacks and has carried on his usual work.

SUMMARY

A case of Menière's syndrome with intermittent but progressive development of vertigo and tinnitus of 10 years duration relieved by surgical destruction of the membranous labyrinth is described. The operative technic used in this case to destroy the labyrinth is briefly outlined.

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BOOK REVIEW

SNAPPER, I.: *Medical Clinics on Bone Diseases*. A Text and Atlas. 2nd Edition. Interscience Publishers. New York, 1949.

The expanding interest in the diseases and dyscrasias of bone which has been evident during the past twenty-five years, and the recognition of their importance to clinical medicine is due the investigations of a handful of men using new laboratory technics to study and re-evaluate a subject which had been considered old and fully formulated at the beginning of the century. The author of this book was one of those men. Out of their studies came the modern integrated science of osteology, that is, the study of bone not only from the viewpoint of anatomy and descriptive pathology, but of bone as an organic system intimately related and responsive to the biology of the entire organism.

The present volume by Dr. Snapper is a greatly enlarged and rewritten version of his original edition which had already earned the place of a classic in its field. First published in Dutch (1937), it was immediately translated into French (1938), thereby entering into the world-read scientific literature. The first American edition did not appear until 1943 after the author had spent some time in China. It contained additional material which he had gathered from his work in Peking. The second edition just released in New York has of course taken cognizance of the large body of recent material accumulated in the active fields of osteopathology and osteophysiology, subjects which are at present under intensive investigation in many leading research centers. One of the chief attractions of the book is the author's superb ability to integrate this material with the older in clear and concise fashion. The absence of irrelevant erudition was a pleasure quite unusual in this type of monograph.

The text as a whole will prove of inestimable value to the general medical reader. It will have added value to the reader whose interest in its problems is special, the serious internist, the pediatrician, orthopaedic surgeon and pathologist. I can think of no special branch of practice or research to which reference to its index will not offer some pertinent data. The material covers the range which its title suggests and includes those lesions of the viscera and glands which produce disturbances in bone metabolism. It does not include certain of the dyscrasias of purely osteogenetic origin since such are apparently not of medical interest and so far have not been linked to systemic dysfunction.

The chapters on hyperparathyroidism, the lipid granulomatoses, the fibrous dystrophies, rickets and osteomalacia, the leukemias, and osteoporosis will be particularly valuable to a large variety of readers. The discussion of the osteofibrous dysplasias in which the author is in some disagreement with other experts is handled with meticulous avoidance of polemic. These passages furnish rare reading in the realm of scientific literature. Those areas where little has been added in recent years, such as Paget's disease and Gaucher's disease, are presented as open subjects with lines for profitable investigation suggested. The author, plowing through the extensive material, is at no time redundant or specious.

The book is as definitive as is possible during a period when so much intensive research is currently in progress. It was a difficult but necessary presentation at this time, and, in the opinion of this reviewer, could not have been more clearly and responsibly written.

EDGAR M. BICK.

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Intratracheal Penicillin Therapy in Suppurative Bronchiectasis. L. E. SILTzbACH. Arch Int. Med., 79: 570, May, 1947.

Thirteen patients with chronic suppurative bronchiectasis and one patient with suppurative pneumonia, atelectasis and early bronchiectasis were treated with intratracheal instillations of penicillin. Ten of the 13 patients with chronic bronchiectasis had a drop of 50 per cent or more in the daily volume of sputum following the instillations. In each case the instillations held the volume of sputum at a lower level than could be maintained previously with the use of sulfonamide drugs, intramuscular injections of penicillin or nebulized penicillin. Three patients had no significant reduction of sputum after the instillations. Recurrence of symptoms was experienced by 4 patients with a favorable immediate response. All recurrences took place within 2 months. Intratracheal penicillin therapy appears to be a useful adjunct in the preparation of patients for lobectomy. It reduces the volume of sputum, renders it less purulent and abolishes the odor. Some patients unsuitable for surgical intervention obtain fairly lasting ameliorative effects from the therapy. One patient with suppurative pneumonia and atelectasis of more than three months' duration experienced immediate and lasting clearing and reexpansion of 2 lobes after intratracheal instillation.

Fluorophotometric Estimation of Stilbamidine in Urine and Blood. A. SALTZMAN. J. Biol. Chem., 168: 699, May, 1947.

By making use of the two readily apparent properties of stilbamidine, adsorption and fluorescence, a simple and accurate method for the determination of stilbamidine in biological fluids was evolved. The stilbamidine is separated from interfering substances by adsorption on a column of Decalco, which is then washed with hot water. Preliminary protein precipitation is not necessary. Elution is carried out with hydrochloric acid-ethanol mixture, which is further acidified to reduce blank fluorescence. The characteristic blue fluorescence of the stilbamidine is then measured in a fluorophotometer. Recovery experiments averaged 87 per cent. Sensitivity down to 1 gamma stilbamidine per cc. of fluid tested.

Pilonidal (Sacroccocygeal) Cyst and Sinus. R. TURELL. New York State J. Med., 47: 977, May, 1947.

The author discusses the etiologic significance of trauma, hyperhidrosis and lack of hygiene in the activation of pilonidal disease. For the treatment of abscess the author advises wide unroofing of the abscess cavity. Small and medium sized pilonidal cysts are effectively closed by simple primary closure technic. For the larger cysts the gluteal fibro-muscular flap operation combined with a proposed delayed closure of the wound is advocated.

The Extracardiac Anitschkow Cell. F. G. ZAK. Anat. Rec., 98: 25, May, 1947.

The cell known as the Anitschkow myocyte is not indigenous to the heart as is generally believed. It was found in the muscle coat of the stomach, the mucosa of the bronchi and the intima of arterioles.

Monoplegia following Carotid Sinus Pressure in the Aged. F. D. ZEMAN AND S. SIEGAL. Am. J. M. Sc., 213: 603, May, 1947.

A man, aged 83 years, with long-standing hypertension, developed a permanent right monoplegia within a few minutes after carotid sinus testing. The literature is reviewed with particular reference to the occurrence of cerebrovascular complications following carotid sinus stimulation. A warning is sounded against the casual employment of carotid sinus pressure either as a diagnostic test or therapeutic measure in aged patients suffering from hypertension and arteriosclerosis. The possible role of the hypersensitive carotid sinus reflex in the precipitation of spontaneous cerebral accidents is discussed. On the basis of this hypothesis, suggestions for the prophylaxis of cerebro-vascular accidents in the aged are outlined.

The Relationship of Trauma to Diseases of the Gastrointestinal Tract. B. B. CROHN. Gastroenterology, 8: 735, June, 1947.

Trauma is recognized as an agent in producing true diseases of the gastrointestinal tract and of other systems of the body. Among the diseases, one may mention cardiospasm, diaphragmatic hernia quite definitely; traumatic duodenal ulcer has been extensively reviewed in the literature and is a not uncommon occurrence. Perforation of pre-existing ulcers as the result of trauma is a common incident as is also hemorrhage from ulcer. In the small intestine there is increasing evidence that ileitis and intestinal granulomata may result from physical injuries. Acute appendicitis of traumatic origin has been much disputed but there are sufficient cases listed in the literature to convince one of the occasional, although rare, occurrence of such a sequence. Diverticulitis of the colon is similarly aggravated and complicated by direct trauma applied to the abdomen. The medico-legal aspects of this problem are important.

Continuous Fever of Intestinal Origin. B. B. CROHN AND H. YARNIS. Ann. Int. Med., 26: 858, June, 1947.

Many cases of continuous fever arise in intestinal infections, namely ileitis and ulcerative colitis. It is remarkable to note how frequently clinicians observing a case of continuous low-grade fever fail to take cognizance of diarrhea when present. Because of joint involvement, eye complications, erythema nodosum and a low leukocyte count, these cases are variously diagnosed as rheumatic fever, brucellosis, periarteritis nodosa, bacterial endocarditis. Barium enema or a barium study of the gastrointestinal tract by mouth will frequently elucidate such cases. The proper medical or surgical treatment following an accurate diagnosis is most satisfactory. The heart complications may either be those of an old true rheumatic fever or those of an acute endocarditis, induced by the intestinal infection where the intestine acts as a portal of entry for bacterial agents.

Otitic Sepsis Due to the Colon Bacillus. Case Report. J. G. DRUSS. Arch. Otolaryng., 34: 687, June, 1947.

Otitic sepsis due to the *Bacillus Coli* is a rare occurrence. It is probably due to the fact that this organism is a relatively infrequent inhabitant of the tympanum. When present, however, it is usually associated with chronic suppurations. A case is reported of an adult female who had a chronic otitis for many years and who, without any clinical evidence of exacerbation, developed a colon bacillus sepsis. The sepsis continued for over a period of 10 months without a primary focus ever being established. In spite of vigorous chemotherapy and the use of penicillin the patient succumbed to meningitis. Post mortem examination disclosed the presence of a huge cholesteatoma of the middle ear which invaded the sigmoid sinus, the labyrinth, petrosa, and intracranial contents. This was

undoubtedly the cause for the unexplained sepsis. That the sulphadiazine and penicillin alone did not effect a cure in this case is not at all surprising since it is well recognized that the colon bacillus is resistant to these drugs, and that these drugs by themselves exert little or no favorable influence on a chronically discharging ear, particularly in the presence of cholesteatoma. The early removal of the focus of infection combined with adequate chemotherapy, however, is still the method of choice in handling these cases.

Selection and Use of Chemotherapeutic Agents. L. EISENBUD. *Ann. Dent.*, 6: 131, June, 1947.

Bacteriologically the mouth is essentially a gram positive sphere. Penicillin, tyrothricin, and the sulfa drugs therefore have a wide field of application in dental practice. Guides to the selection of the most effective antibiotics for any particular infection are discussed. Dosages and methods of administration are enumerated. Mixed infections of the mouth are common, and since some organisms, even staphylococci, may be resistant to the action of small doses of penicillin, the minimum amount prescribed for any patient with an acute infection is 500,000 units daily, administered intramuscularly.

Some Characteristics of Gastric Secretion Induced by Mustard Oil Suspension. F. HOLLANDER, F. U. LAUBER AND J. STEIN. *Am. J. Physiol.*, 149: 724, June, 1947.

It was found that a 1 per cent aqueous mustard oil emulsion is a poor stimulus for gastric mucus secretion, in comparison with agents previously studied. However, this agent is an active mucosal irritant yielding large volumes of a serous transudate. The persistently low viscosity, opacity, columnar cell content, and probable small mucin content indicate that mustard oil fails to evoke the usual responses of a mucus stimulus. These properties of the secretion together with its plasma-like appearance and frequent occurrence of blood suggest, however, a transudate or exudate. Undoubtedly, some mucus is present but the proportion seems to be small.

Management of Whooping Cough with Special Reference to Infants. J. L. KOHN AND A. E. FISCHER. *Am. J. Dis. Child.*, 73: 663, June, 1947.

A description is presented of the regimen employed in hospital management of 887 infants with whooping cough, 475 being under 6 months. Diagnosis was established by the clinical picture, culture of *Hemophilus pertussis* with nasopharyngeal swab, and leukocyte count. Chest roentgenograms were taken if pneumonia or atelectasis was suspected. Method of treatment:—1. Nursing. Seriously ill infants should be attended at all times. Personnel should be trained in the use of airways, suction and oxygen. 2. Oxygen therapy. All children seriously ill with whooping cough have some measure of anoxia, most commonly due to obstruction to the respiratory tree by tenacious secretion. On hospitalization, therefore, every infant is placed in an oxygen tent. The paroxysms become shorter and less exhausting, and patients with convulsions are rapidly relieved. The duration of oxygen therapy depends upon the infant's general condition, and presence of pneumonia and atelectasis. Oxygen concentration is maintained at 50 per cent, humidity at 40 per cent and the temperature at 68° F. 3. Aspiration. Exhausted infants have difficulty in expelling secretions which accumulate in the respiratory tract. Relief may be obtained by frequent postural change and aspiration of the pharynx and trachea. The pharynx should be aspirated during severe paroxysms. 4. Medical therapy. Expectorants and antispasmodics are of limited value. Sedatives are occasionally used. Sulfadiazine and penicillin help to control secondary infections. 5. Parenteral therapy. Fluids, blood and plasma are used when necessary. 6. Feeding. Feedings are small and frequent. Gavage is avoided because of the danger of stimulating paroxysms and vomiting. The child is always fed in a recumbent position in the nurse's arms. Following the feeding, the infant is placed on the side and suction applied through the nose. If a severe paroxysm follows feeding, the child is placed in a sitting position with head held forward and the pharynx aspirated if necessary. 7. Human "hyperimmune" and rabbit serums. Of 887 infants treated in this manner, over a period of 6 years, the mortality varied from 3.5 to 6.7 per cent.

Treatment of Duodenal Ulcers. Partial Gastrectomy Versus Palliative Resection. R. LEWISOHN. J.A.M.A., 134: 571, June, 1947.

The term "partial gastrectomy for duodenal ulcer" should be used only when the gastric resection includes the removal of the duodenal ulcer. If the duodenal ulcer is left *in situ* the operation should be classified as palliative resection. The term "subtotal gastrectomy" implies that a small pouch of stomach remains after the gastric resection. It should never be used in describing gastric resection for duodenal ulcer, which does not remove more than one half or two thirds of the stomach. In order to guarantee a complete removal of the pylorus and a safe closure of the duodenum, the resection should be carried below the ulcer. I strongly advise against the technic which leaves the ulcer *in situ*. Such a procedure is apt to be followed by an increase in immediate postoperative complications and an increased incidence of jejunal ulcers. Abdominal drainage is unnecessary and inadvisable in most cases. It indicates that the surgeon is not satisfied with the safety of the duodenal suture. In most bleeding duodenal ulcers the hemorrhage stops spontaneously or after a few transfusions. However, in a small percentage of these cases, partial gastrectomy must be employed as the only possible procedure in an attempt to save the life of the patient.

Reiter's Disease—Report of a Case Successfully Treated. J. D. MATIS. New York State J. Med., 47: 1274, June, 1947.

There has been a recent trend to more frequently recognize the triad of symptoms consisting of urethritis, arthritis, and conjunctivitis as Reiter's disease. The non-specific etiology of each of the symptoms is explained. The polyarthritis usually is the most chronic and incapacitating of the symptoms. Various drugs have been tried in the treatment of Reiter's disease without success. Large doses of penicillin and sulfonamide drugs alone and in combination, had been used by others and the author without response. The author describes a 21 year old white soldier who was admitted to an Army hospital in France with the diagnosis of Reiter's disease. The conjunctivitis and urethritis cleared spontaneously, but the left knee, left elbow, and left shoulder remained swollen and painful after six weeks of hospitalization, in spite of penicillin, sulfadiazine and salicylates. Fever therapy by means of typhoid vaccine in a slow intravenous drip was then resorted to. The patient had a temperature sustained at 102° to 103.2° F. for over four hours and during this time sulfadiazine and penicillin were administered concomitantly. Four days after treatment there was the first marked improvement in the patient's condition. The involved joints improved remarkably and patient was ordered out of bed. During his military career the author had similar gratifying results with fever therapy in cases of Reiter's disease other than the one described.

Acute Suppurative Phlebitis Complicated by Septicemia. H. NEUHOF AND G. P. SELEY. Surgery, 21: 831, June, 1947.

Suppurative phlebitis is a common cause of septicemia. In the prepenicillin period, suppurative phlebitis was a common cause of fatal septicemia; in the present period it is often in an abortive form because of penicillin therapy. The diagnosis of suppurative phlebitis producing septicemia must often be made on indirect evidence: an inflammatory focus, chills, and positive blood culture. Drainage of the suppurative focus will not suffice unless there is added thereto adequate excision of the main involved venous trunk, the combination of these procedures resulted in cure in 87.5 per cent of cases. In the penicillin era fewer cases will be encountered in which surgical considerations will arise. In penicillin resistant cases or in cases of partial results, drainage and excision of the main involved venous trunk should be performed.

Diagnosis of Generalized Amyloidosis by the Congo Red Test: Definitive Diagnostic Criteria. I. J. SELIKOFF. Am. J. M. Sc., 213: 719, June, 1947.

The Congo red test is based on the removal of intravenously injected dye from the blood stream by amyloid substance, if this be present. Where only small deposits are present,

there will be failure to absorb appreciable amounts of Congo red (0-89 per cent absorption). Patients without amyloidosis give similar results: the test is thus not diagnostic in this absorption range. Patients showing 90-100 per cent absorption usually have amyloidosis, but occasionally a single test with this result will occur without amyloidosis ("false positives"). Clinical studies reported show that a patient should not be considered definitely amyloid unless there is complete or nearly complete absorption on 2 consecutive Congo red tests. When this has occurred, further retest has always remained positive and no patient showing this has yet come to post-mortem without showing amyloidosis.

Influence of Early Experiences upon the Formation of the Personality. A. ADLER. *Nervous Child*, 6: 318, July, 1947.

A report about the way by which a child reacted to *one* incident may prove of greater value for the evaluation of his personality than an elaborate narrative account of a multitude of events during his life, "traumatizing" as they may seem to be. No fact can be considered "traumatizing" unless it can be proved, through the reaction of the child to the event, that it actually traumatized the child. It is unlikely that a one time incident is able to exert any lasting effect upon a child. Observations show that unless a continued attitude on the side of the parents has been impressed upon the child for a longer period, single events, "traumatic" as they may seem to be, are dealt with by the child in a way which conforms to the child's previous pattern.

Cleansing of Sensitive Skin, with Determination of the pH of the Skin Following Use of Soap and a Soap Substitute. E. T. BERNSTEIN. *J. Investigative Dermat.*, 9: 5, July, 1947.

The effect of soapless detergents on the pH of the skin, was determined in experimental studies. The pH was taken on two symmetrically-located skin areas before each washing procedure, whereupon both areas were washed for one minute each: with Lowila soap cake and water on one site and with ordinary toilet soap and water on the other. The washed areas were rinsed with tap water and dried with paper towels. Contact of one test area with material used for the procedure on the other test area was carefully avoided. In this way, 50 test series were carried out. The result of these investigations was that washing with the final detergent cake produced only a very moderate and comparatively transient increase in pH on the skin, unlike the marked and more persistent rise following the use of soap. Results of a representative experiment are as follows:

pH of flexor aspect of forearm before washing, 3.8

	pH of skin washed with Soap Lowila cake	
1 minute after washing	7.0	4.2
5 minutes after washing	6.5	3.8
12 minutes after washing	6.5	3.8
30 minutes after washing	6.2	3.8
40 minutes after washing	4.5	3.8
60 minutes after washing	4.2	3.8
70 minutes after washing	4.0	3.8

The Relative Value of Several Diagnostic Tests for Chronic Simple Glaucoma. S. BLOOMFIELD AND L. KELLERMAN. *Am. J. Ophth.*, 30: 869, July, 1947.

The 6 tests most commonly employed to establish the diagnosis of chronic simple glaucoma in doubtful eyes were studied to determine their relative value. For this purpose they were individually applied to a large group of patients known to have that disease, but with normal ocular tension, although all medication had been temporarily discontinued. Thus, these patients simulated those in whom the disease is suspected but unproven. The results obtained indicated that the lability test of Bloomfield and Lambert is the most reliable. The water drinking test, the diurnal tension curve, the dark room test, the caffeine test, and the mydriatic test with paredrine proved less dependable in that descending order.

Sinistroposition: A stigma of Relative Infertility. R. T. FRANK. *Am. J. Obst. & Gynec.*, 54: 88, July, 1947.

A hitherto overlooked and undescribed congenital stigma is "sinistroposition" of the uterus, which is found in some relatively infertile women. The uterus is found closely applied to the left pelvic wall due to a short left parametrium. 83 patients showed these anatomical findings. In 13 the condition was produced secondarily by birth trauma, inflammations or post operatively. Of the 30 married primary sinistropositions, only one had born children.

The Use of Penicillin in Surgical Infections. A Note of Warning. J. GARLOCK. *New York State J. Med.*, 47: 1604, July, 1947.

The indiscriminate use of penicillin is condemned. When penicillin is administered during the course of acute cholecystitis, the symptoms and physical signs may improve although the pathological process may continue to advance. Thus, while the observing physician has a false sense of security, the cholecystitis may proceed to gangrene and perforation before the urgency of operation is realized.

Permanent Metachromatic Staining of Mucus in Tissue Sections and Smears. M. HESS AND F. HOLLANDER. *J. Lab. & Clin. Med.*, 32: 905, July, 1947.

A technique is described for metachromatic staining of smears of gastric secretion as well as tissue sections from various portions of the gastrointestinal tract. The metachromatic effect produced is permanent; it does not fade nor deteriorate as preparations by former methods do. The procedure's primary value is its specific differentiation of mucus and mucinous material from cytoplasm and other cell structures. The methods for fixing and staining the preparations are described in detail. The superiority of the present technique may be ascribed to the alkaline pH of the staining and washing fluids. As a result, cytoplasmic destruction in smears is eliminated.

Rapid Method for Seeding Nail Cultures. A. KURTIN AND R. YONTEF. *Arch. Dermat. & Syph.*, 56: 112, July, 1947.

A method for using the electric hand drill on infected nails to rapidly seed a culture medium is demonstrated.

Inositol Content of Blood Plasma. S. SONNE AND H. SOBOTKA. *Arch. Biochem.*, 14: 93, July, 1947.

It has been suggested that inositol exerts an adjuvant effect upon the utilization of orally administered tocopherol. Thus, inositol may be of importance for the therapeutic efficacy of tocopherol in amyotrophic lateral sclerosis. The inositol situation in these patients and the influence of inositol ingestion on the blood level was studied. The hitherto unknown range of serum inositol in normal subjects and patients was determined by application of the nephelometric micro bioassay with *Saccharomyces carlsbergensis*. The range of plasma inositol in normals and certain patients was found to be 0.37–0.76 mg./100 ml. for individual fasting samples. Pooled plasma from miscellaneous patients ranged from 0.54–1.87 mg./100 ml. Daily ingestion of 1.50 g. of inositol usually produces a moderate rise of the plasma inositol level. Destruction of some inositol during acid hydrolysis cannot be excluded. The state of inositol in the plasma needs further investigation.

Clinical and Pathologic Studies in Sprue. D. ADLERSBERG AND J. SCHEIN. *J.A.M.A.*, 134: 1459, August, 1947.

Forty cases of the sprue syndrome were reported, which were divided into 2 groups comprising 36 patients with primary and 4 with secondary sprue. The clinical differentiation of the 2 types of sprue was possible on the basis of duration of symptoms, presence of typical oral and lingual lesions, characteristic hematologic changes and response to therapy. The gastrointestinal observations were essentially similar in the 2 groups, as was a chemical

analysis of blood, duodenal contents and feces. Postmortem examination was performed in 10 cases, in 9 of which there were noteworthy findings and in 1 of which complete study was not possible. The pathologic changes consisted of unique findings in intestinal villi (hyaline band formation) and mesenteric glands (disproportionate trabeculation). Amyloid involvement of the small intestine was observed in 2 instances. Abdominal lymphosarcomatosis and intestinal lipodystrophy each occurred once. Pigment deposition (hemo-fusein) was encountered in 2 instances in the small intestine, and extreme steatosis of the liver was observed once. In 4 of the 6 patients whose disease was designated as primary sprue there were varying degrees of pancreatic fibrosis which were not accounted for by biliary disease. The possible relationship of the pathologic changes to sprue has been discussed.

Vasospasm Associated with Multiple Sclerosis. R. M. BRICKNER AND C. R. FRANKLIN.
Arch. Neurol. & Psychiat., 58: 125, August, 1947.

Observations on 18 patients with multiple sclerosis who showed constrictions of some of the retinal arterioles are reported. In one case constriction was seen in a retinal venule. The observations are summarized as follows: (a) The constrictions appear as isolated areas of narrowing in limited parts of arterioles; in hourglass form; and in segmented form (broken columns of blood were seen in the vessels, with white areas between them). In addition, alternating opening and closing of an arteriole were seen in 3 cases. In 1 instance constrictions kalcidoscopically appeared and disappeared in the whole arteriolar tree while the examination was proceeding. Pulsations of the whole arteriolar tree were seen occasionally. (b) Scotomas were usually associated with the constrictions, and sometimes there was also reduction in visual acuity. The objective findings coincided with the patient's subjective complaints. Some patients complained of a shimmering of the object seen, which caused its outlines to be blurred. (c) In most instances in which they were employed, fast-acting vasodilating drugs caused prompt, temporary reduction of the constrictions and of the size of the scotomas (sometimes to zero). In several instances there was an increase of visual acuity as well. The drugs used were amyl nitrite, administered by inhalation, and papaverine hydrochloride, administered by vein. (d) In 4 cases with early or transient diplopia, the degree of diplopia was reduced by the inhalation of amyl nitrite. (e) The intention tremor in 2 cases was increased by the smoking of a cigaret. In 1 case, the intravenous injection of papaverine hydrochloride prevented this effect; the imbibing of liquor also prevented it and transiently abolished the basic intention tremor as well. (f) Constrictions and scotomas were both found frequently to be multiple and to shift in position.

The constrictions are regarded as spasms.

The hypothesis is developed that the lesions throughout the central nervous system in multiple sclerosis are caused by diminution of the blood supply which results from the spasms.

Evidence is presented which suggests the existence of two types of grades of scotoma and of diplopia—one transient and affected by vasodilating drugs; the other fixed and unaffected by the drugs. The two types may merge and be revealed jointly in one symptom. When the transient part is reduced by the drugs, the fixed part remains. The hypothesis is proposed that the fixed lesions result from a vasospasm either more complete or of longer duration than the vasospasm responsible for the reducible symptom. The reducible symptom is interpreted as a consequence of transient or incomplete spasm which permits the passage of sufficient blood, promptly or swiftly enough, to preserve the life of the tissue, but which, nonetheless, impairs function; the dilation of the vessel by the drug permits the temporary reestablishment of normal nutritional conditions and the disappearance of the reducible symptom.

Attention is called to the frequency of sudden, brief attacks of minor, as well as major, symptoms in multiple sclerosis. In this series, attacks of visual disturbance are recorded as precipitated by heat (hot baths, hot drinks, sitting under a hot air dryer), by eating,

by emergence from the dark into strong light and by emotional disturbance. In 2 cases the smoking of a cigaret caused exaggeration of the intention tremor. This evidence suggests that some of the vessels (presumably previously "sensitized" in some way) may become constricted by reflex action.

It is pointed out that the transient improvements in function could not have been due to spontaneous remissions, for they followed administration of the drugs immediately and regularly. It is quite possible that the sudden attacks of scotoma which occurred in some cases were actual attacks of multiple sclerosis. In many of these there were known precipitating causes. It would seem possible that many people might have such slight attacks as these at various times of their lives, in which the process is actually that of multiple sclerosis but which are not repeated and which do not result in fixed lesions. Such attacks might never come to the attention of the family physician or the neurologist. If the hypotheses outlined are correct, two possible types of "spontaneous" remission would appear to be possible in the regular course of multiple sclerosis. One type could result from disappearance of vasospasms which were responsible for disturbances of function without permanent injury to tissue. "Acute remissions" of this type, although transient, appear to have occurred in these experiments. The other type could follow the healing of actual lesions in the central nervous system.

No satisfactory evidence is available to explain the vasospasms.

Clinical Evaluation of Vascular Damage in Diabetes Mellitus. H. DOLGER. J.A.M.A., 134: 1289, August, 1947.

In cases of diabetes of 25 years' duration, not one of 200 patients examined regularly escaped retinal hemorrhage, regardless of age of onset, severity of diabetes, or type of treatment used. Retinopathy usually presaged progressive vascular degeneration. Fifty per cent presented hypertension and albuminuria at the time of the earliest retinal hemorrhage. Present-day treatment of diabetes has failed to avert the accelerated vascular damage, which is an associated phenomenon of the disease and not a "complication."

Studies in Fetal Metabolism. W. H. GOLDWATER AND DEWITT STETTEN, JR. J. Biol. Chem., 169: 723, August, 1947.

Isotope tracer studies on the fetuses of pregnant rats in late gestation indicate that fatty acids and cholesterol cross the rat placenta. The rat fetus also synthesizes glycogen, fatty acids, and cholesterol at rates appreciably higher than the corresponding rates in adult animals. Fetal synthesis and deposition of glycogen per day approximately equals the amount present in the fetal organism. Evidence obtained suggests that epinephrine crosses the rat placenta, and that fetal glycogen is subject to its glycogenolytic stimulus. Insulin injected into the pregnant rat seems to affect fetal constituents only thru decreased availability of maternal glucose and increased supply of small organic fragments derived therefrom.

Successful Desensitization in Penicillin Sensitivity. S. M. PECK AND S. SIEGAL. J.A.M.A., 134: 1546, August, 1947.

Penicillin is finding increasingly wide use in present day medical practice. The clinical indications for its use were at first almost exclusively imperative and urgent. However, at present it is used in preference to other available forms of treatment in many mild infections, and its administration has become an almost routine postoperative precaution. As a result, the reported incidence of reaction to penicillin has increased. In a white man aged 63 there developed an erythematovesicular eruption after the parenteral administration of penicillin. This first appeared on the hands, feet and groin, and it rapidly became generalized. The presence of a positive delayed skin test to penicillin and the re-elicitation of the eruption on subsequent use of the drug, indicate that the first eruption was due to penicillin sensitivity. Successful desensitization, which permitted the administration of penicillin in effective dosage, is described.

In Vitro Effect of Penicillin upon Toxins of Clostridium Welchii, Type A. S. S. SCHNEIERSON. J. Immunol., 56: 307, August, 1947.

The effect of penicillin upon the toxins of *Clostridium Welchii*, Type A was investigated. Unlike the antitoxin, 10,000 units of penicillin failed to inactivate or neutralize in vitro the hemotoxin, lecithinase, necrotoxin or lethal toxin of *Clostridium Welchii* type A filtrate.

Concentrated Aqueous Heparin, A New Form of Intramuscular Administration. D. STATS AND H. NEUFELD. *Am. J. M. Sc.*, 214: 159, August, 1947.

An aqueous form of heparin containing 100 mg. of the drug per c.c. was administered intramuscularly for its anti-coagulant effect in 115 patients. The dose required for this effect varied between 100 and 175 mg., given at 8 or 12 hour intervals. The only toxic effects observed were in recently operated cases where hemorrhage at the site of operation was observed if the heparin was started within 2½ days of the operation. The frequency of complications at the site of injection was extremely low.

Hemolytic Anemia Associated with Malignant Diseases. D. STATS, N. ROSENTHAL, AND L. R. WASSERMAN. *Am. J. Clin. Path.*, 17: 585, August, 1947.

The clinical summaries of 10 cases of hemolytic anemia associated with chronic lymphatic leukemia, Hodgkin's disease, giant follicular lymphoblastoma, lymphosarcoma and Boeck's sarcoid are presented. The points discussed with relation to the subject consisted of the findings in the peripheral blood and bone marrow in pathological changes in the spleen, the occurrence of spontaneous remissions and the influence of splenectomy, radiotherapy and blood transfusions on the underlying disease. There is such a marked variation in the clinical and laboratory findings and in the response to therapy, that rules for management of such cases could not be categorically stated.

The Lability Test for Chronic Simple Glaucoma. S. BLOOMFIELD. *Arch. Ophth.*, 38: 368, September, 1947.

A new test is described by which the diagnosis of chronic simple glaucoma may be established earlier and more certainly than has been possible in the past. It is a combination of jugular compression and the cold pressor test whereby transient rises in intraocular tension are produced that are distinctly abnormal in eyes with chronic simple glaucoma. A study of the results of this test when applied to 29 eyes with this disease, and 77 normal eyes, has established the reliability and convenience of this diagnostic method.

A Synthetic Aliment for Feeding by Gastro-intestinal Fistula Which Is Predigested and Nutritionally Complete. F. HOLLANDER AND H. A. SOBER. *Am. Coll. Surgeons*, New York, September, 1947.

Several years ago, a diet for feeding jejunostomy patients for several weeks was devised in this laboratory. Subsequently, this predigested aliment was used for more prolonged periods in patients with anorexia nervosa and cicatricial stenosis of the esophagus with gastrostomy, as well as those with jejunostomy. To improve its nutritional quality for such prolonged use, and also its stability and ease of preparation, the aliment has been modified to consist of the following: 1. a dry sterilized mixture of protein hydrolysate, dextrins, maltose, whole liver substance, and a special salt mixture; 2. an aqueous emulsion of corn and Haliver oils; 3. sterile water; and 4. a suitable preparation of the water-soluble vitamins. This aliment has been the sole source of nourishment for 19 months in a patient with jejunostomy for completely obstructed esophagus, and during this period he gained 45 lbs.

Correlation of Physiological and Clinical Observations Following Vagotomy for Peptic Ulcer.

F. HOLLANDER, V. WEINSTEIN AND F. U. LAUBER. *Am. Coll. Surgeons*, New York, September, 1947.

Gastric secretion studies were carried out on a series of cases of gastric, duodenal and gastrojejunal ulcers treated by bilateral vagotomy (vagotomy), alone or combined with gastroenterostomy or subtotal gastric resection. These included pre- and post-operative acidity data obtained from the insulin test, and the gruel or histamine tests, as well as from fasting (night) secretion. Clinical observations are analyzed in relation to these data.

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THE BELA SCHICK LECTURE

SEARCHING FOR NEW CHEMOTHERAPEUTIC AGENTS—A
TRAVELOGUE*

SELMAN A. WAKSMAN, PH.D.

*Department of Microbiology, New Jersey Agricultural Experiment
Station, New Brunswick, N. J.*

I am not going to present an address of the kind that an audience of this nature is usually accustomed to hear, namely, on a clinical subject. This will be rather a travelogue, a travelogue into the unknown field of microbes.

How does one go about looking for organisms that are capable of producing chemical agents which the clinician could use in combating various infectious diseases? As you well know, there are known at present two approaches to chemotherapy, or rather two general procedures for finding new chemotherapeutic agents. First is the synthetic approach of the chemist: the brilliant investigations of Ehrlich, who discovered the potentialities of salvarsan and other arsenicals, used primarily in combating spirochaetal and protozoan diseases, and, more recently, the discovery of the various sulfonamides used in combating a number of bacterial infections. Secondly, there is the approach of the microbiologist: the biologist, or naturalist, first learned from practical observations and from natives of the efficacy of certain plant derivatives, such as quinine, for combating certain infections; today, the microbiologist has taken up the search; he has thus entered into a new field, that of antibiotics.

What are antibiotics? Before I describe to you the approach of the microbiologist in his search for new antibiotics, which could be used as chemotherapeutic agents, I should like first to define "antibiotics," to describe their properties and to indicate how they differ from the ordinary antiseptics and disinfectants.

Antibiotics are highly selective in their action upon microorganisms; the selectivity extends not only to genera or species of bacteria sensitive to certain antibiotics, but to bacterial strains and even to individual cells. Some antibiotics will attack largely gram-positive bacteria and only to a very limited extent the gram-negative forms, whereas others will act alike upon representative groups within both of these two major groups of bacteria. Some have no effect upon filamentous fungi, others attack both fungi and bacteria, and still others attack only fungi. Some are active against rickettsiae, and a few can attack the larger viruses. Some possess anti-protozoan activities, and others act upon trichomonads. Unfortunately, there are no antibiotics yet known that would be active against the smaller viruses, although there are indications that such may be

* From the Department of Microbiology, New Jersey Agricultural Experiment Station, Rutgers University—the State University of New Jersey.

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found in time. These variations in the activities of antibiotics upon different microorganisms are not only qualitative but also quantitative in nature. Thus we may speak of an antibiotic spectrum, that is, the selective action of a given antibiotic upon a number of representative bacteria and other microorganisms. This is illustrated in Table 1, where the antibiotic spectra of two antibiotics isolated in our own laboratory are presented.

TABLE 1
Comparative antibacterial spectra of neomycin and streptomycin (S)
Amounts required to inhibit growth of organism in 1 ml of culture

ORGANISM	NEOMYCIN	STREPTOMYCIN
	$\mu\text{g/ml}$	$\mu\text{g/ml}$
<i>Aerobacter aerogenes</i>	0.625	0.5-2.5
<i>Bacillus mycoides</i>	0.1-0.5	0.1-3.8
<i>B. subtilis</i>	0.02-0.1	0.12-1.0
<i>Brucella abortus</i>	1.25-5.0	0.5-3.75
<i>B. melitensis</i>	0.625-2.5	0.5
<i>Clostridium perfringens</i>	>10.0	>104
<i>Corynebacterium diphtheriae</i>	0.156	0.375-3.75
<i>Escherichia coli</i>	1.25-2.5	0.3-3.75
<i>Haemophilus influenzae</i>	1.25-2.5	1.56-5.0
<i>H. pertussis</i>	2.5	1.25-3.0
<i>Klebsiella pneumoniae</i>	0.312-0.625	0.625-8.0
<i>Mycobacterium avium</i>	0.1-0.3	10
<i>M. tuberculosis</i>	<0.5	1.0-5.0
<i>M. tuberculosis</i> R	<0.5	>100
<i>Pasteurella pestis</i>	0.625	0.75-1.5
<i>P. tularensis</i>	0.156	0.15-0.3
<i>Phytomonas pruni</i>	0.1	0.25
<i>Proteus vulgaris</i>	1.25-2.5	0.4-3.0
<i>Pseudomonas aeruginosa</i>	12.5-25.0	2.5-25.0
<i>Salmonella typhosa</i>	0.1-0.625	1.0-37.5
<i>S. schattmülleri</i>	0.4-0.7	2.0
<i>Sarcina lutea</i>	2.5	0.25
<i>Serratia marcescens</i>	1.25	1.0
<i>Shigella paradysenteriae</i>	0.25-0.5	0.25-3.75
<i>Staphylococcus aureus</i>	0.156-0.625	0.5->16.0
<i>Streptococcus faecalis</i>	5.0	50.0
<i>Vibrio comma</i>	2.5	6.0-37.5
Various fungi	>10.0	>10.0

The second major characteristic of antibiotics is their variation in structure. They do not represent a single chemical compound, but a great variety of compounds, ranging from relatively simple substances containing only carbon, hydrogen and oxygen to the more complex forms which contain also nitrogen, sulphur and even chlorine. Antibiotics vary greatly in chemical structure. Some antibiotics are not single entities, but comprise several groups of compounds which may differ only in certain minor variations in their chemical structure and in their antibacterial activities, as is the case of the penicillin group of anti-

biotics. Some microorganisms are capable of producing more than one antibiotic. This was well demonstrated long ago for *Pseudomonas aeruginosa*, which forms not only pyocyanase and pyocyanin, but also such compounds as pyo-group and pyolipic acid. *Aspergillus flavus* forms aspergillic acid and one type of penicillin. The streptomycin-producing organism, *Streptomyces griseus*, forms not only streptomycin and mannosido-streptomycin, but also actidione and streptocin, whereas other strains of this organism may form other antibiotics or none at all. The streptomycin-producing species gives rise to mutants, which possess different antibiotic-forming potentials.

I hope that I have given you enough illustrations to emphasize that we are dealing here with a property of certain organisms which may change not only quantitatively, but even qualitatively. On the other hand, the same antibiotic may be produced by different organisms. Penicillin is formed not only by *Penicillium notatum* but also by *A. flavus* and certain other fungi. The same is true of the production of streptomycin, clavacin and various other antibiotics. Because of this property and since the antibiotic is frequently named after the organism producing it, several names may be attached to the same substance. The nature of the medium and conditions of growth will also influence the nature and concentration of the antibiotic formed by a given organism.

Some antibiotics, as penicillin, are destroyed rapidly by various microorganisms, whereas others as streptomycin are highly resistant to microbial activity. The mode of action of antibiotics upon bacteria differs; this is highly significant, because the future of chemotherapy depends upon a proper understanding of the action of these antibiotics on the bacteria and, therefore, upon our ability to imitate that effect by the synthesis of suitable chemical compounds which would possess the same or similar properties.

Antibiotics vary greatly in their toxicity to animals. Some, like penicillin, are only slightly toxic. Others may show certain limited toxic effects, like streptomycin, which is responsible for a vestibular disturbance in some patients. Still others, like actinomycin, are very highly toxic. Some antibiotics can be modified chemically to reduce their toxic properties. In the case of streptomycin, for example, a derivative has been produced, known as dihydrostreptomycin, which is a reduced form of streptomycin and which is apparently less toxic to the animal body. Finally, bacteria sensitive to a given antibiotic may gradually develop resistance to it when allowed to be in contact with it for some time. Here again, different antibiotics show marked differences, some, like streptomycin, allowing rapid development of resistance of sensitive bacteria (Table 2). Others, like penicillin, will allow only gradual development of resistance and only of certain few sensitive bacteria. The process of reacquirement of sensitivity or loss of resistance also differs with the antibiotic, as well as with the bacteria.

You will thus recognize even from a mere listing of these properties of antibiotics that they would vary greatly as potential chemotherapeutic agents. This is largely the reason why out of more than 100 antibiotics that have been isolated during the past ten years, only 5 or 6 so far have found practical application in the treatment of various infectious diseases.

How would a microbiologist proceed in isolating an antibiotic substance and in establishing its chemotherapeutic potentialities? I should like to take you through the laboratory and illustrate the various stages involved in the isolation of an antibiotic.

Let us begin with the soil. I have here a bit of soil, highly magnified. You will recognize that the soil is not a dead mass, but is teeming with life. Actually one can recognize filaments of fungi and actinomycetes surrounding the soil particles. Since I am going to deal in this lecture to a large extent with the actinomycetes, it is essential to recognize that these organisms grow abundantly in the soil, making up 10 to 50 per cent of all the organisms capable of developing on the agar plate.

At least 8 or 10 distinct steps are involved in the process of isolating an antibiotic substance. The first step consists in plating out the soil. The second consists in isolating and culturing the different forms developing on the plate. The third stage comprises the testing of the organisms for their antimicrobial properties.

TABLE 2

Survival of E. coli in plates containing varying concentrations of neomycin and streptomycin (8)

INCUBATION OF PLATES	NEOMYCIN (μ /ML)				STREPTOMYCIN (μ G/ML)			
	2	4	6	8	2	4	6	8
	Colonies developing on plate from 1 ml of bacterial suspension*							
<i>hrs.</i>								
24	700	8	0	0	21,000	270	20	0
48	1,500	65	1	<1	4,600,000	560	70	26
72	1,700	108	2	<1	6,700,000	640	130	70
120	1,700	108	2	<1	7,400,000	640	130	70

* 1 ml of 24-hour-old bacterial suspension contained 246 million cells.

The fourth involves the growth of the organism in liquid media, and subsequent testing of the culture filtrate. The fifth and sixth steps involve removal of the substance from the medium and its subsequent concentration and purification. The seventh step deals with the establishment, by microbiological tests, of the identity of the isolated substance with the active material present in the original medium. The eighth, ninth, and tenth stages involve the study of the toxicity of the preparation, its activity in experimental animals, and finally its clinical application.

These procedures may vary greatly depending upon the materials from which the organisms are isolated, the nature of antibiotic involved, and available laboratory facilities and personnel. Frequently, a change in method of growing a given organism may involve changes in methods of handling. You will recall that when penicillin was first produced in this country, a bottle process was used; later, the submerged process was introduced. In other words, we are not limited by a given procedure for growing the organism. I have not even mentioned the tremendous possibilities for improving the yield of a given antibiotic by the further

selection of strains, by the development of new culture media, and by improving conditions of growth. Since different antibiotics vary in their chemical properties, the methods of isolation will vary greatly. We may adsorb the active material on charcoal or on some other adsorbent and then remove it with acid-alcohol or an organic solvent. We may remove the substance directly from the medium by means of solvents.

The isolation of antibiotics thus involves the services of the microbiologist, the chemist, the pharmacologist, the physiologist, the clinician, and finally the

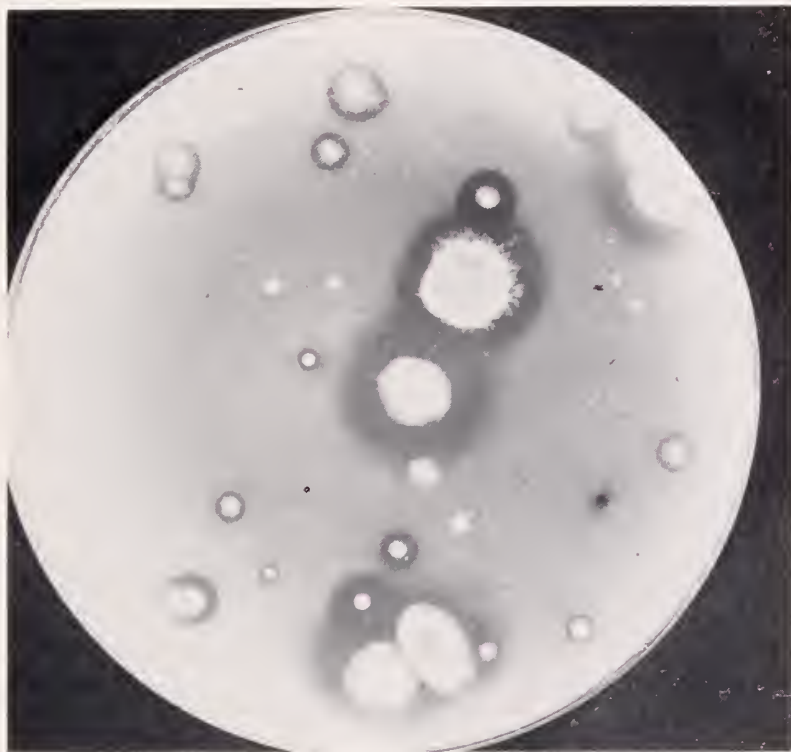


FIG. 1. Production of clear zones on a bacterial plate by an antibiotic-producing organism.

manufacturer. The collaboration of different investigators is thus required. The microbiologist may start with thousands of organisms. The chemist may end up with a dozen substances. The pharmacologist may approve of only one or two, which may finally come to clinical evaluation. A tremendous background of research, selection, comparison and testing is thus involved, before a product is placed in the hands of the clinical investigator.

Every general microbiologist and certainly the soil bacteriologist and the plant pathologist have frequently observed that certain colonies developing on an agar plate are surrounded by clear zones of inhibition of bacterial growth. The great importance of this phenomenon was not recognized, however; it was

usually referred to as a case of staling of the medium, or the liberation of some "lethal principle," or by some similar term; these observations were soon forgotten as far as their potential practical significance is concerned.

Gradually, it became recognized, however, that we are dealing here with a fundamental principle in microbiology. This is true particularly of Fleming's observation in 1928 on the production of an antibacterial agent by a green fungus, later identified as *P. notatum*. He designated this agent as *penicillin*.

I need not take your time to review the historical development of our present concept of antibiotics. I should like to outline further some of the procedures



FIG. 2. Appearance of an antibiotic-producing actinomycetes on a bacterial agar plate.

that are used at present in the isolation of antibiotics. An agar plate is inoculated with a suspension of bacteria, let us say *Staphylococcus aureus*, and a dilute suspension of soil is added to the inoculated agar before it has solidified. This plate is incubated at 28°C. Certain organisms growing out of the soil produce a clear zone around their colonies where the growth of the staphylococcus is inhibited (fig. 1). These organisms produce antibiotics active upon the latter. Most of the soil organisms show no zones, however. Some of the zone producers are fungi, others are actinomycetes (fig. 2, 3, 4), still others are bacteria. These colonies are picked and streaked upon fresh agar plates. The streak is allowed to grow for 24 or 48 hours, and various test bacteria are streaked toward it, as

shown in Figure 5. This will tend to confirm not only the antibacterial properties of the active agent, but also its selective action upon different bacteria or its antibiotic spectrum. We are thus able, by simple procedures to learn rapidly what the particular antibiotic promises to be. We can then decide whether subsequent steps of growth, isolation and further testing are justified. It is not merely a question of finding organisms which are highly effective against bacteria or other microorganisms, but also of determining their selective activity. A new agent that is no better than penicillin is hardly worth wasting our time on at present.

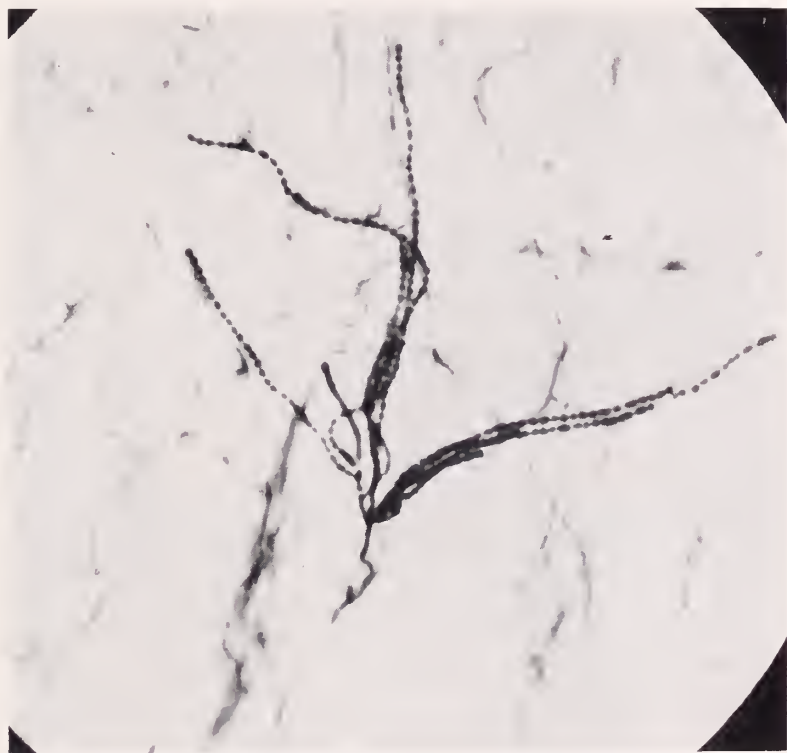


FIG. 3. A typical antibiotic-producing actinomycetes, *Streptomyces antibioticus*

Since the isolation of streptomycin in 1943-1944, we have been largely concerned with a search for organisms that produce antibiotics active against those bacteria which are or which have become resistant to streptomycin. For this purpose, we may use as test organisms streptomycin-resistant strains. We are thus able to determine at once whether we are dealing with a type compound in which we are particularly interested at present. In this period of about 5 years we must have examined some 50,000 cultures and isolated several antibiotics. Of these, neomycin appears to be the most suitable for our purposes. All the streptomycin-resistant cultures are sensitive to it to the same degree as the corresponding streptomycin-sensitive culture. This could be easily established

by the use of streptomycin-resistant strains of test bacteria (Table 3). On the other hand, streptomycin-dependent strains did not grow at all in the presence

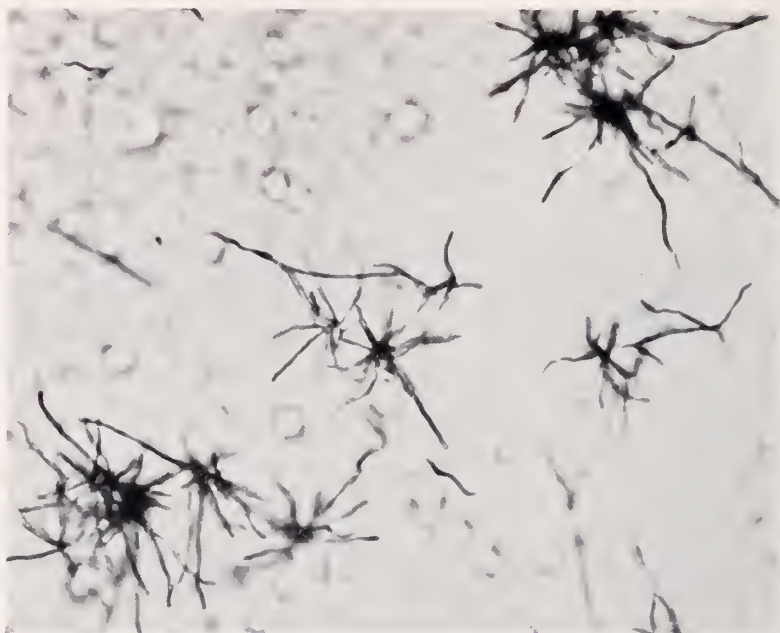


FIG. 4. Another antibiotic-producing actinomycetes, *Streptomyces griseus*, streptomycin-producing strain.



FIG. 5. Antibiotic effect of *Streptomyces lavendulae*. The test bacteria reading from left to right: *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Bacillus mycoides*, *Sarcina lutea*, *Serratia marcescens*.

of neomycin, thus proving that the two antibiotics are not related to each other (fig. 6).

TABLE 3

Comparative effects of neomycin and streptomycin upon the growth of different mycobacteria (7)
Growth inhibition in units per ml after 14 days' incubation

TEST ORGANISM	NEOMYCIN	STREPTOMYCIN
<i>M. avium</i>	0.1-0.3	10.0
<i>M. tuberculosis</i> H37Rv	0.2-1.0	1.0-5.0
<i>M. tuberculosis</i> H37RvR*	0.2-1.0	>5,000
<i>Mycobacterium</i> 607	0.1	0.2-0.4
<i>Mycobacterium</i> 607R*	0.25	300

* R = streptomycin-resistant strain.



FIG. 6. Antibiotic spectra of *Streptomyces griseus* (I, III) and *Streptomyces fradiae* (II, IV). Test bacteria for I and II, reading from top down: *Escherichia coli*, *Bacillus mycoides*, *Staphylococcus aureus* and *Bacillus subtilis*. For III and IV, *E. coli*-streptomycin-sensitive, *E. coli*-streptomycin-resistant R₁, *E. coli*-streptomycin-resistant R₂, *E. coli*-streptomycin-dependent strains.

By means of a carefully selected group of test bacteria, it is possible to identify unknown antibiotics produced by freshly isolated organisms. Suppose an unknown organism produces an antibiotic which is not active against streptomycin-resistant strains and favors the growth of streptomycin-dependent strains; it must be streptomycin or one of its derivatives. The use of special bacterial cultures which have been made resistant to a given antibiotic, for the purpose of identifying new antibiotics, has placed a new and highly useful tool in the hands of the investigator. By means of those and other methods, it has been possible to establish that a large number of organisms, found among the fungi, bacteria, and actinomycetes, are capable of producing antibiotics. This property is not characteristic of the family, or of the genus or even of the species, but only of certain strains within a given species. Let me give you a few illustrations.

The filamentous fungi are known to produce a large number of antibiotics. The first of these was isolated in 1895 and designated as *mycophenolic acid*, and the last in 1949 and designated as *candidulinc*. Between these two extremes, we find a large number of compounds, including *gliotoxin*, *penicillic acid*, *fumigacin*, *gladiolic acid*, *clavacin* or *claviformin*, *chctomin*, *aspergillic acid*, and most important of all, *penicillin*. These substances vary greatly in their antibiotic spectra, chemical properties, toxicity, activity *in vivo* and chemotherapeutic potentialities. Of these, only penicillin has found wide practical application. In addition to the lower fungi, the higher or mushroom fungi are also capable of producing certain antibiotics. The most important of these is *clitocybin* which was reported to have a marked effect upon the tuberculosis organism.

The bacteria as well produce a large number of antibiotics. The spore-forming bacteria produce tyrothricin, which is a mixture of gramicidin and tyrocidine; bacitracin; subtilin; polymyxin; aerosporin; and a number of others. The non-spore-forming bacteria produce pyocyanase, pyocyanin, prodigiosin, nisin, colicines, and a variety of others. Of these, only tyrothricin, bacitracin, and possibly polymyxin and nisin, have found practical application in the control of certain infections in man and in animals.

Finally, we come to the actinomycetes, a group of organisms to which I have devoted most of my own life-work. (It was actually 35 years ago this month that I began as a senior at Rutgers to study the actinomycetes as a part of a larger project on the "Bacteria, actinomyces and fungi of the soil.") When we first took up, in 1939, the study of the formation of antibiotics by these organisms, there were only two antibacterial preparations known to have been produced by certain species, *actinomycetin* and *actinomyces lysozyme*, neither of which was a true antibiotic, and neither was well understood. The first substance that we isolated in 1940 was designated as *actinomycin*. This was a nitrogenous ring compound, pigmented orange, and highly toxic. It is produced by a large number of actinomycetes, and has since been reported from all parts of the world. The next important compound that we isolated in 1941, was designated as *streptothricin*. This was much less toxic and highly effective, both *in vitro* and *in vivo*, against infections caused by gram-negative and other bacteria. Upon further study, it was found to have a delayed toxic effect upon experimental

animals. Before it reached the clinical stage, however, we isolated, in 1943, *streptomycin*. This antibiotic appeared to supplement penicillin in combating various bacterial infections, penicillin acting largely upon those diseases that are caused by gram-positive bacteria, cocci and spirochaetes, and streptomycin upon those produced by gram-negative and acid-fast bacteria. Still, streptomycin had certain limitations, notably the effect upon the vestibular condition of some of the patients and the potential development of resistance upon prolonged contact with the antibiotic (Table 4). Other agents were soon discovered in other laboratories; most important of these were *chloromycetin* and *aurcomycin*, especially because of their activity upon rickettsiae and some of the larger viruses; more recently, we isolated *neomycin*, the potentialities of which have not been established as yet. We might say truthfully that since penicillin, the most important antibiotics have been isolated from actinomycetes. A recent tabulation

TABLE 4

Influence of continuous incubation upon the antimycobacterial properties of different antibiotics (7)

ORGANISMS	UNITS OF ANTIBIOTIC REQUIRED TO INHIBIT GROWTH PER MILLILITER OF CULTURE IN DUBOS-TWEEN MEDIUM*					
	Neomycin		Streptomycin		Streptothricin	
	Days of incubation					
	7	14	7	14	7	14
<i>Mycobacterium</i> 607	0.1	0.1	0.3	0.3-0.6	0.75	?
<i>Mycobacterium</i> 607R	0.1-0.25	0.25	200	300	1.0	?
	14	28	13	28	14	28
<i>M. tuberculosis</i> H37Rv.	0.5-1.0	1.5-2.0	2	4	10	20
<i>M. tuberculosis</i> H37RvR.	1.0	1.0	>5,000	>5,000	10	20

* Dilution of inoculum = 1:1,000.

demonstrated that no less than 30 antibiotics are now known to be produced by actinomycetes.

The mere isolation of a proper organism producing a desirable antibiotic is only the first step in the isolation of such agents. Next comes the problem of development of suitable media for the cultivation of the organism and the production of the antibiotic. At this stage we are still dealing with crude culture preparations and, therefore, we know nothing of the chemical properties of our new antibiotic. There is still a long way to go before the active substance is isolated in a pure state. The concentration of the new antibiotic is measured by its ability to inhibit bacterial growth; meanwhile, information is gained concerning its nature by its selective action upon different bacteria. At each step of isolation and purification, this selective activity upon different bacteria and other microorganisms is kept definitely in mind, to be sure that we are still dealing with the same substance, and have not gone off on a tangent, since the

organism producing it is a biological system, which varies in nature, and which may give rise, under different conditions of cultivation, to other antibiotics different from the one originally found. There have actually been instances where an investigator was led to the isolation of a substance totally different from the one originally present in the medium or the one that he was originally interested in, simply because he had to measure the potency of the isolated material by its antibacterial activities, and the significance of the antibiotic spectrum of such material was not sufficiently recognized (fig. 7).



FIG. 7. Antifungal action of a soil actinomycete. Test organisms: *Trichoderma* sp., *Trichophyton mentagrophytes*, *Fusarium* sp. *Penicillium luteum-purpurogenum*.

Next to the qualitative method of testing unknown antibiotics, the quantitative method is most important. Here as well, until a suitable chemical procedure for measuring the concentration of the substance has been developed, we must depend upon the activity of the antibiotic upon the growth of a certain test organism. The turbidimetric method measures the rate of growth of the test organism in liquid media, and the cup method measures the rate of diffusion of the antibiotic in solid media by the zone of inhibition produced. The selection of the test organism is most important in this connection. Some antibiotics, such as the various penicillins, are characterized by the ratios of inhibition of growth of different test bacteria.

Once the medium is selected and the method of evaluation decided upon, the problem of growing the organism on a large scale comes into the picture. Here the chemical engineer, or perhaps better the bacteriological engineer, has rendered a tremendous service in translating the results from flasks into large 3,000 to 15,000 gallon fermentors. The problem of aeration and the problem of contamination have been challenging, but they were successfully overcome.

Removal of the antibiotic from the liquid medium, and its subsequent purification and isolation in crystalline form, involve a number of important problems, which are largely the domain of the chemist rather than the microbiologist. The collaboration of the two is most important, however, for reasons presented previously. The isolation of penicillin and the elucidation of its chemical structure and of its chemotherapeutic potentialities will stand as a monument to the successful collaboration of chemists and microbiologists, government and industry, individual initiative and group investigations, not only on a national but on an international scale, since they involved the collaboration of investigators in Great Britain and in this country. Who can argue after this that the solution of certain important problems does not depend upon that type of collaboration? The isolation and the studies on utilization of streptomycin were not carried out on so grand a scale, but, here as well, they involved the collaboration of a small group in a small University laboratory, a large Industrial organization, and an important Clinic, before the potentialities of this antibiotic were recognized.

Since each antibiotic represents a different type of chemical entity, the chemist has to devise in each case new methods for isolation and purification. He may use adsorbents, such as charcoal, zeolites, or resins, for removal of the substance from the large volume of medium, or he may use solvents, such as ether, chloroform or alcohol, to extract it directly from the medium. He may use the paper or zeolite chromatogram, for separating the various antibiotic entities. Sooner or later, he may succeed in crystallizing the compound and in determining its chemical structure. This is usually followed by an attempt at synthesis. So far, the chemist has been successful in only three cases, of which only one proved to be of practical value. The antibiotics so far synthesized are clavacin, penicillin and chloromycetin, only the last one being used for the manufacture of the antibacterial agent, which has been designated as *chloramphenicol*.

Once the antibiotic has been isolated, whether in a crude or in a highly purified state, the study of its toxicity and its *in vivo* activity has to precede its clinical application. This involves many problems, as the painful efforts of the pharmacologist can bear out. We must not forget the role of the control division of the Food and Drug Administration, which is requested by law to place its stamp of approval on any new drug before it can be used in the treatment of human infections. The path is a long one, but if the end is satisfactory, it offers ample compensation for all the effort expended.

Throughout these many steps, the part played by the microbiologist is an important one. He is concerned with the isolation of the antibiotic-producing organism, with the development of suitable media, with the testing of the active substance, and finally with the study of the mode of action of the antibiotic

upon sensitive bacteria and with a variety of other problems, such as the development of resistance among bacteria against a certain antibiotic. Numerous theories have been proposed to explain the action of antibiotics upon bacteria, ranging from surface tension effects to interference with cell division and with certain metabolic reactions. Different antibiotics may not affect the same nutrition mechanism. Streptomycin, for example, has been shown to affect the amino acid synthesis of bacteria. In some cases, certain enzymatic mechanisms are involved.

Finally, to elucidate how we proceed with the study of a certain problem and to indicate how long it took us before this problem was brought, not to a satisfactory solution, but to a stage where further developments could easily be foreseen, let us consider our own work on *Mycobacterium tuberculosis*. Ours was primarily a soil microbiological laboratory. We were hardly interested in the study of animal pathogens and certainly not of such apparently specialized and rather resistant forms as the tuberculosis organism, which involved problems that have been intensely studied during the last six or more decades by many eminent bacteriologists, chemists and clinicians.

In 1932, Dr. W. C. White of the National Tuberculosis Association came to see me to discuss the fate of the tubercle organism in the soil. I agreed to accept a fellowship sponsored by the National Research Council, and selected one of my graduate students to undertake this study. After feeding living and dead bacteria to soils and sewage, for nearly 3 years, we reached the conclusion that these bacteria do not survive in the soil very long. In this respect we merely confirmed observations made previously by other investigators. We further observed that certain organisms inhabiting the soil or sewage, notably protozoa, were possibly responsible for this phenomenon. We were not interested at that time in antibiotics, and were thus not prepared to follow up these observations or to associate them with the broader principle of microbial antagonism.

About 6 years later, in 1941, Dr. White called together a small conference in this city. This conference was attended by Dr. Gardner of the Trudeau Sanatorium, by one or two other medical investigators, two or three industrial representatives, and myself. The purpose of the meeting was to discuss ways and means of attacking the problem of chemotherapy of tuberculosis. To my great amazement, the suggestion was made that we must look for enzyme systems that would dissolve the tubercle organism. When I raised the question as to what type of enzymes we must look for, it was suggested that possibly proteolytic enzymes might be made to work. Dr. White brought forth an illustration by citing the earthworm, which was said to be capable of digesting these bacteria. When I questioned this approach, and emphasized the fact that to digest the tough cells of the tuberculosis organism, an enzyme would have to be highly potent and might, therefore, have an undesirable effect upon the body tissues. Dr. White turned to me rather impatiently, and said, "Well, now, how would you go about solving this problem?" My answer was, "I don't know, but what I would like to look for is not a digestive or proteolytic mechanism, but an agent that would influence the synthetic reactions of the cells or cell division, in other

words an antibiotic mechanism." This conference did not go beyond a general discussion. I promised that, since we were actively engaged at that time in the study of antibiotics, we would in time investigate the effect of these agents upon the tubercle organism. With the discovery of streptothricin and later of streptomycin, we actually succeeded in isolating such mechanisms and we, therefore, at once concentrated upon this problem. These studies soon attracted the attention of Dr. Feldman and Dr. Hinshaw of the Mayo Clinic, who immediately offered us their facilities for testing the effect of these antibiotics upon experimental, and later upon clinical, tuberculosis.

Streptomycin was later found not to be an ideal agent, it certainly was not the looked for "cure" for this "white plague" of mankind. It had its definite limitations. However, the great potentialities in the field of antibiotics for the control of tuberculosis were established. It was merely a question of searching for other agents that would be free of those limitations and tend to supplement

TABLE 5

Comparative effects of neomycin and dihydrostreptomycin upon mice infected with dihydrostreptomycin-resistant S. aureus (6)

NUMBER OF MICE	DILUTION OF CULTURE	TREATMENT	UNITS PER MOUSE	SURVIVAL OF MICE IN DAYS				PER CENT SURVIVAL
				1	2	4	10	
10	10 ⁻²	Controls	—	0	—	—	—	0
10	10 ⁻³	Controls	—	0	—	—	—	0
10	10 ⁻⁴	Controls	—	10	8	8	7	70
10	10 ⁻²	Dihydrostreptomycin	50	0	—	—	—	0
10	10 ⁻²	Dihydrostreptomycin	1,000	10	9	9	9	90
10	10 ⁻²	Dihydrostreptomycin	5,000	10	10	10	9	90
4	10 ⁻²	Neomycin	12.5	4	4	4	4	100
4	10 ⁻²	Neomycin	25	4	4	4	4	100
4	10 ⁻²	Neomycin	50	4	4	4	4	100

streptomycin. An antibiotic recently isolated in our laboratory, which we designated as *neomycin* appears to offer great promise in this respect. Had this antibiotic been discovered 10 years ago, it probably would have proved an ideal chemotherapeutic agent. Now with penicillin, streptomycin, and several other antibiotics in practical use for the control of infections caused by gram-positive and gram-negative bacteria, acid-fast bacteria and rickettsiae, a new agent must be either much superior, or much more effective against bacteria in general, or it must be active against those organisms which are resistant to the other antibiotics.

Certain pertinent data pertaining to the action of neomycin, as compared with streptomycin (Tables 1-6), reveal that this antibiotic has certain highly desirable properties, in addition to its high potency against the tuberculosis organism and various other bacteria. One of these is its activity against organisms that are resistant to streptomycin. The fact that it favors less the development of resistance among sensitive bacteria than streptomycin does is also of

great importance. Both antibiotics possess not only bacteriostatic but also marked bactericidal properties. Both are very stable to the action of micro-organisms, and both are favored by an alkaline reaction.

Finally, I would like to compare our present knowledge of antibiotics as chemotherapeutic agents with that of only four and a half years ago. When I delivered the Harvey lecture in this very city, on November 16, 1944, I attempted to list the various human and animal diseases in nine groups, and to indicate which of these could be effectively treated with antibiotics. A similar list prepared at the present time can better illustrate the progress that has been made in this very short period than anything else that I can present to you. The

TABLE 6
Effect of neomycin upon E. typhosa (6)

NUMBER OF MICE	DILUTION OF CULTURE	TREATMENT	UNITS PER MOUSE	SURVIVAL OF MICE IN DAYS						PER CENT SURVIVAL
				1	2	4	6	8	10	
10	10 ⁻²	Controls	—	0	—	—	—	—	—	0
10	10 ⁻³	Controls	—	0	—	—	—	—	—	0
10	10 ⁻⁴	Controls	—	5	1	—	—	—	—	0
10	10 ⁻⁵	Controls	—	6	6	3	0	—	—	0
10	10 ⁻²	Streptomycin	25	1	0	—	—	—	—	0
10	10 ⁻²	Streptomycin	50	9	7	4	3	1	1	10
10	10 ⁻²	Streptomycin	100	10	10	7	1	—	—	0
10	10 ⁻²	Streptomycin	200	10	10	6	3	1	1	10
10	10 ⁻²	Streptomycin	400	10	10	9	7	5	5	50
10	10 ⁻²	Neomycin	6.25	1	1	1	1	1	1	10
10	10 ⁻²	Neomycin	12.5	9	8	7	5	4	2	20
10	10 ⁻²	Neomycin	25	10	10	9	5	2	1	10
10	10 ⁻²	Neomycin	50	10	10	10	10	9	8	80
10	10 ⁻²	Neomycin	100	10	10	10	10	10	9	90

diseases on which antibiotic therapy has succeeded can be divided into the following groups:

1. *Diseases caused by gram-positive bacteria and certain gram-negative cocci.* The organisms causing these diseases are highly sensitive to various antibiotics. The various penicillins have been used extensively in the treatment of these diseases. The tyrothricin complex and bacitracin have found application in the treatment of wound infections and other diseases caused by some of these bacteria. Organisms that become resistant to penicillin, or strains naturally resistant to this antibiotic, may still be sensitive to bacitracin or to streptomycin, or to several other antibiotics active upon these bacteria. This group of diseases may, therefore, be considered as having been successfully combated by the use of penicillin and other antibiotic agents.

2. *Diseases caused by gram-negative bacteria.* These bacteria are for the most part resistant to penicillin, tyrothricin, and bacitracin, but they are sensitive to several other antibiotics. One of these, streptomycin, has found extensive application in the treatment of numerous diseases caused by gram-negative organisms.

Polymyxin, aureomycin, and neomycin are other highly promising agents. The use of two antibiotics or of an antibiotic, such as streptomycin, with a synthetic compound, as sulfathiazine, will tend to overcome the rapid development of resistance of some of the bacteria to streptomycin. This has been done successfully in the treatment of certain forms of brucellosis and in a variety of other infections.

3. *Diseases caused by acid-fast bacteria.* These diseases were once believed to be among the most resistant to chemotherapy. *M. tuberculosis* responds with a high degree of sensitivity to many antibiotics *in vitro*. Of these, only streptomycin has so far been found to be effective *in vivo*. When supplemented with para-amino-salicylic acid or some of the sulfones, streptomycin has sometimes been found to be even more effective, especially in overcoming the rapid development of resistance. There are other promising agents, such as neomycin.

4. *Spirochaetal diseases.* Several antibiotics, notably penicillin, have a remarkable effect upon diseases caused by spirochaetes. The use of penicillin in the treatment of these infections appears to be gradually superseding the methods of treatment current before the advent of antibiotic therapy.

5. *Rickettsial diseases.* A number of antibiotics are now known to be highly effective against rickettsiae. This is true particularly of chloromycetin and aureomycin, which promise a final solution in the treatment of the diseases caused by these organisms.

6. *Virus diseases.* Although no antibiotic has yet been discovered which can be used successfully against diseases caused by the typical or small viruses, such as those of the common cold or polio, some of the larger viruses, such as psittacosis, lymphogranuloma and certain types of virus pneumonia, are sensitive to several antibiotics.

7. *Fungus diseases.* A number of antibiotics have been found capable of attacking fungi. This is true of gliotoxin, clavacin, streptothricin, actidione and antimycin. One or more of these may find application in the control of some of the animal and plant diseases caused by fungi.

8. *Protozoan diseases.* Various protozoa capable of causing human infections are subject to attack by antibiotics. This is true, for example, of the action of streptocin upon trichomonads, although the therapeutic significance of this has not been established as yet.

9. *Tumors.* Although no effective antibiotic is known at present which could be used for combating infections caused by foreign cells, such as tumors, certain bacteria, fungi (*A. fumigatus*), and protozoa are able to attack tumors and may in time yield promising agents.

Chemotherapy has made rapid progress since the days of Ehrlich. The microbiologist and the chemist, by contributing the antibiotics, have placed in the hands of the clinician powerful tools for the treatment of numerous infections, many of which did not lend themselves previously to therapy. When the final chapter of this rapidly expanding field of science is written, the last decade of 1939-1949 will truthfully be designated, as Dr. Tillett so aptly put it, as the "antibiotic age."

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MAXILLO-FACIAL TRIAD AND ITS CORRECTIONS*

IRVING B. GOLDMAN, M.D.

The term, maxillo-facial triad, is proposed to designate a facial deformity resulting from nasal trauma in early childhood, which presents characteristic and interrelated features. The nose is crooked with a marked posterior deviation of the septum, which is usually dislocated anteriorly, causing a twisted tip and columella; the palate is high and arched; and the chin recedes, and in advanced cases frequently gives the bearer the appearance commonly referred to as "bird face" (figs. 1, 2 and 3).

ETIOLOGY AND PATHOGENESIS

The harmonious skeletal development of the face results from the effect of the opposing and balancing action of two sets of muscles. The external facial muscles which because of their tone tend to lengthen the facial skeleton are counteracted by the muscles of the tongue that tend to spread the facial structures laterally. Alteration in this harmonious development caused by nasal obstruction due to a badly deflected septum incurred during the process of development results in the maxillo-facial triad.

A marked septal deflection will cause mouth breathing and as the open mouth interferes with the lateral pressure of the tongue, the unopposed action of the facial muscles causes the normal flat arch of the palate to assume a Gothic shape. This in turn results in dental distortion, misplacement and irregularity of the teeth, malocclusion and overbite. The muscular disharmony is not only limited to the palate, but also to the mandibular muscles, and may result in microgenia or micrognathia.

The history in each instance of such maldevelopment is characteristic. Early in life the nose is injured; it is followed by nasal obstruction and deflection of the nose. No attempt is made to reset the displaced parts. As the child grows and approaches adolescence the external and intranasal deformities and retrusion of the lower jaw become more noticeable. The features usually due to nasal obstruction and resulting mouth breathing become apparent: the upper lip becomes retracted upward, the alveolar margins instead of being shaped like a horse-shoe take on a hairpin curve, the face assumes a somewhat stupid languid expression (fig. 4).

MANAGEMENT

Obviously the prophylactic treatment is of greatest importance. Once the deformity has developed, the best that can be offered is some restorative work for the chin: cartilage, bone implants, or frequently the material left over from the reconstruction of the nose may be utilized for building out the chin.

* From The Otolaryngologic Service, Division of Rhinoplasty, The Mount Sinai Hospital, New York.

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FIG. 1. A. F. Age 25. Injured nose in early childhood. Complained of marked nasal obstruction. Intranasal examination showed the septum to be deviated to right posteriorly and dislocated to the left anteriorly. The palate was narrowed and arched. The teeth were irregular.

A. Anterior view showing crooked nose corrected by simultaneous rhinoplasty and submucous resection. B. The post-operative photograph was taken 16 days after operation. The patient resided a good distance from N. Y. and had to return to business, so there was some postoperative swelling of the nose.



FIG. 2. A. Basal view showing twisted tip and columella. Note the caudal dislocation of the septum which occluded the left nostril. B. Plastic correction of the septum resulted in improved nasal physiology.



FIG. 3. A. Lateral view showing the markedly underdeveloped receding chin. B. Chin corrected at the same time as the rhinoplasty was done.



FIG. 4. H. P. Age 7. Injured nose two years previously. No attempt was made to correct the deformity. Examination showed a crooked nose and a badly deflected septum causing nasal obstruction. He is scheduled for correction.

Anterior and lateral views showing the crooked nose. Note the open mouth and languid expression.

Nasal reconstruction will eliminate another element of the triad. The palatal defect must be left to the orthodontist who, by placing stresses on various teeth, may alter the shape of the palate, if it is not seen too late in the development of the facial skeleton.

It must be recognized that from the moment of the very first respiration at birth, one of the most potent influences upon which jaw expansion and development depends is the physiological action of correct respiration. Nasal and septal injuries are prone to follow obstetrical delivery with or without use of forceps. Therefore, it is advisable that soon after birth the position of the septum be ascertained and realigned if the septum has been dislocated from the crest or vomer.



FIG. 5. M. C. Age 21. Nose injured at the age of 6. No attempt was made to reduce the fracture. Intranasal examination showed the septum to be deviated to the right posteriorly and angulated to the left anteriorly, blocking the entrance of air to both right and left nasal chambers.

A. Anterior view showing the crooked nose. B. Results of simultaneous submucous resection and rhinoplasty.

Fractures of the nasal bones and deflections of the septum in infancy and childhood should be reduced at once. This will prevent future disfigurements. The septum can be repositioned and reconstructed, the nasal bones can be reset. Deformities that have not been repaired at the time of injury and cause obstructive symptoms which do not respond to local therapy should be corrected at an early age. These measures became possible only in the past few years with the development of new plastic concepts and technique. Prior to the time when the otolaryngologist became interested, there was no procedure caring for this deformity. As a matter of fact, the dictum was to let the child go to maturity before operation. Today, ventilation of the nasal chambers is made feasible by modern plastic procedures on the septum which do not interfere with its development.

If left untreated the disturbance in nasal physiology results not only in the before-mentioned maxillo-facial disfigurements but may cause disturbed chest



FIG. 6. A. Lateral view showing microgenia. B. The defect corrected by submental insertion of patient's hump.



FIG. 7. A. Basal view showing dislocated septum accompanied by a deviated tip. B. Appearance after correction.

architecture with increased tendency to pulmonary infection. In addition, it predisposes the sinuses and ears to infection and undermines the general well being.

Correction of the maxillo-facial triad should be carried out as a single proce-

ture whenever possible. I have been successful in correcting the septum while simultaneously carrying out repair of the nasal deformity. Various plastic procedures on the septum and/or a combination of techniques have to be employed. In many cases, it is necessary to remove the caudal portion of the septum completely and replace it with the patient's own cartilage or isograft if one is to obtain a straight tip and columella (figs. 5, 6, & 7).

The micrognathia is corrected by a submental incision through the skin, subcutaneous tissue and muscle. A pocket is prepared in front of the mandible and a graft inserted. The graft may be the patient's hump, the hump with layers of removed septal cartilage, preserved cartilage, or cancellous bone graft obtained from the hip. The cartilage grafts are held in position by silk mattress sutures, the bone by stainless steel sutures through holes drilled in it. The wound is closed with atraumatic sutures.

CONCLUSION

Triple facial deformities involving the nose, palate and chin resulting from nasal trauma early in childhood, for which the term maxillo-facial triad is proposed, can be corrected by a single operation. In addition to facial maldevelopment, orthodontic problems can be obviated by early examinations and immediate care in nasal or septal injuries. A deflected septum causing nasal obstruction in childhood which does not respond to conservative management ought not be deferred for operation until maturity but should be corrected by plastic procedures which will not interfere with but rather aid in its already impeded development and thus avoid deflection from the harmonious development of the face which may lead to the formation of the maxillo-facial triad.

A CHORIONEPITHELIOMA OF THE INFUNDIBULUM WITH DISCRETE HEMIC METASTASES IN POSTERIOR LOBE OF THE PITUITARY¹

GERALD F. PERRY, M.D.

In repeated surveys of chorionepithelioma its frequent occurrence in females has been emphasized. However, the acceptance of a primary chorionepithelioma of the testicle is relatively recent. Moreover, extragenital chorionepitheliomas in the male are found to be rare, as only 26 such cases had been reported up to 1945 (1). The occurrence of chorionepithelioma in the male is explained by unilateral differentiation of the primordial epithelium found in teratomas.

The frequency with which all chorionepitheliomas metastasize has been stressed by all investigators. Failure to find the original seat of such a tumor is said to be due to the fact that it may be so small and symptomless as to be easily overlooked or may regress and disappear long before metastases are discovered elsewhere in the body (4). It is fully accepted that most chorionepitheliomas found in extragenital regions of the male are metastatic lesions from a primary tumor of the testis.

Several authors have reported the presence of metastatic chorionepitheliomas in the brain coincident with similar lesions elsewhere in the body (2, 3, 4, 5, 6, 7, 8). Three other cases of chorionepitheliomas were described as primary. In all these cases it is difficult to exclude the possibility of a preexisting testicular tumor for reasons mentioned previously (1, 9, 10). The presence of a primary chorionepithelioma in the brain has yet to be established.

Pollason and Violet (7) in their collection of 455 chorionepitheliomas occurring in females found that a little over 9 per cent had metastasized into the brain. No similar figures have been worked out for these tumors in the male, but, from the numerous reported cases an equal incidence may be assumed.

The material studied in the Neuropathology Laboratory of The Mount Sinai Hospital during the past ten years contains three cases of chorionepithelioma in the brain. In two instances the tumors were found in men at the extremely divergent ages of 70 and 22. In the older man there was a widespread metastasis throughout the organs of the body and a small hemorrhagic neoplastic nodule in the right occipital lobe. Tumor cells were also found in the posterior lobe of the pituitary. The second case serves as the object of this study.

CASE REPORT

History. A man, aged 22 years, first noted the gradual onset of excessive thirst and urination in May 1947. He drank two glasses of water every hour and passed an equivalent amount of urine. He noticed in June that he was gaining in weight although his food intake remained the same. At that time he noticed a blurring of vision intermittently every 5 to 10 minutes while working as a lithographer. The vision worsened steadily and objects were blurred constantly. Two days before coming to the hospital he developed a generalized headache which lasted two hours and was relieved by aspirin. He entered the hospital on August 8, 1947.

¹ From the Neuropathological Laboratory, The Mount Sinai Hospital, New York.

Examination. The general physical examination revealed no significant findings.

A neurological examination showed the pupils reacting sluggishly to light. There was a decreased visual acuity (V.O.D., 20/200; V.O.S., 20/100), temporal pallor of both optic discs and bitemporal hemianopsia.

Laboratory data. Cerebrospinal fluid was xanthochromic after centrifugation; with 9,000 red blood cells per cubic mm.; Pandy, 4 plus; total protein, 254 mg. per cent; Wassermann



FIG. 1. Sections through the tumor mass. The tumor mass is seen to fill the third ventricle, fuse with the underlying tuber cinereum and invade the thalamus on the right side. Anteriorly, the tumor mass spreads over the optic chiasm. The lateral ventricles are elevated and reduced to narrow slits on both sides.

and colloidal gold negative. Blood: Wassermann, negative; cholesterol, 360 mg. per cent; and cholesterol esters, 190 mg. per cent. A glucose tolerance test revealed a flat curve, dropping to 35 mg. per cent after 3 hours. Urine: specific gravity, 1.002, rising to 1.020 after injection of pitressin. X-ray studies of the chest, skull and long bones were negative. Arteriography: left carotid arteriogram was normal. Electroencephalography indicated diffuse cerebral dysfunction. There was no indication of any focal lesion in the hemispheres. Basal metabolic rate was minus 5 per cent.

Course. Following arteriography the patient developed delirium and fever up to 104°F. A right transfrontal craniotomy was performed on September 7, 1947 but no lesion could be seen in the chiasmal region. Post-operatively the patient reacted poorly. He showed marked psychomotor overactivity and repeated manneristic motor patterns. He developed Cheyne-Stokes respirations and died on September 14, 1947, approximately 20 days after admission into the hospital and one week following operation.

Post mortem findings. The autopsy was limited to the head.

Gross. The brain was voluminous. There was some flattening of the convolutions and the consistency seemed to be increased. At the base of the brain the optic chiasm appeared swollen. The right optic nerve was enlarged while the left was somewhat flattened. The optic tracts were separated by the markedly protruding tuber cinereum. It had a brownish-red coloration and it was resistant to the palpating finger. The mamillary bodies were not discernible, and seemed to be fused with the swollen tuber cinereum. The pituitary was

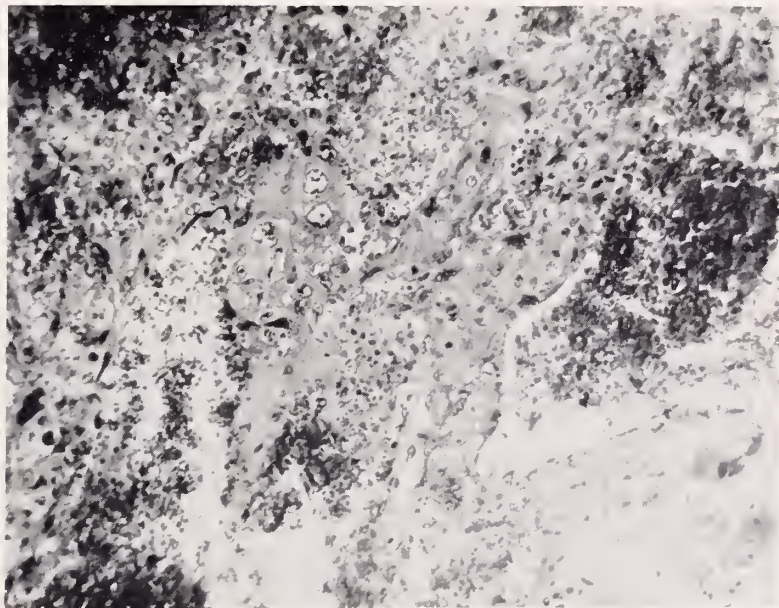


FIG. 2. The tumor tissue simulating villus formation is seen projecting into large blood sinuses. Elongated syncytial cells may be seen forming the outer layer of the projected tissue. Photomicrograph, hematoxylin and eosin stain, $\times 100$.

flattened in its vertical dimension but otherwise appeared normal. The vessels at the base of the brain were not unusual.

On sectioning, a large mass was found completely filling the third ventricle, leaving only a small opening posteriorly at the transition from the third ventricle to the aqueduct (fig. 1). The mass was inseparable from the underlying tuber cinereum. In fact, the tuber cinereum and the tumor mass appeared to be identical. The mass was at some points fairly clearly separated from the enveloping third ventricle on the left side, but, on the right, the tumor infiltrated the adjacent wall of the third ventricle, extending into the thalamus and part of the internal capsule. Anteriorly, on a level with the anterior commissure, the tumor could be seen as an encapsulated mass with its covering spreading over the anterior portion of the optic chiasm. The fornix anterior to the tumor was somewhat softened. The cut surface of the tumor showed it to be soft and highly vascular, with reddish-brown mottling intermingled with pinkish-gray areas. The ventricular system was elevated. The lateral ventricles were reduced to narrow slits with the wings spread out in both directions, with a moderate dilatation of the ends of the anterior horns.

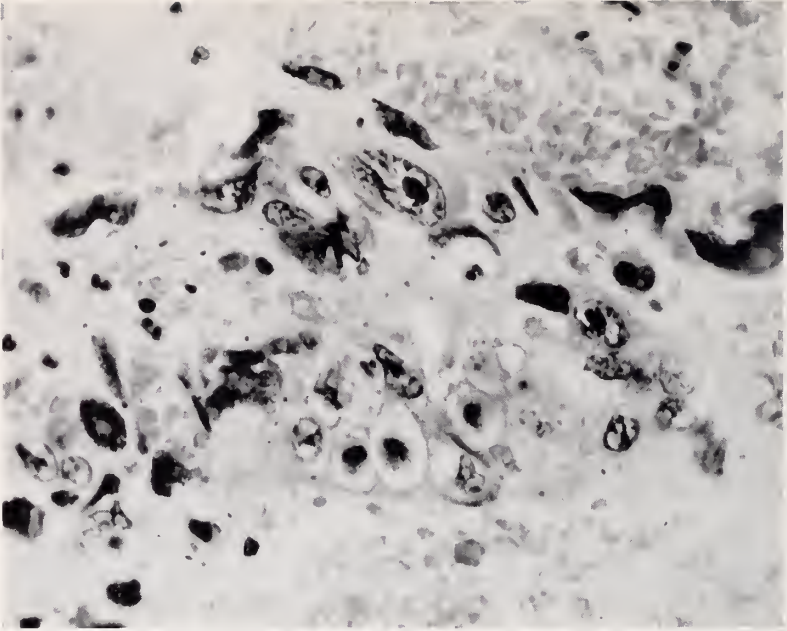


FIG. 3. The same section as in Figure 2, $\times 500$. The arrangement of the synektial and Langhans' cells is better illustrated.

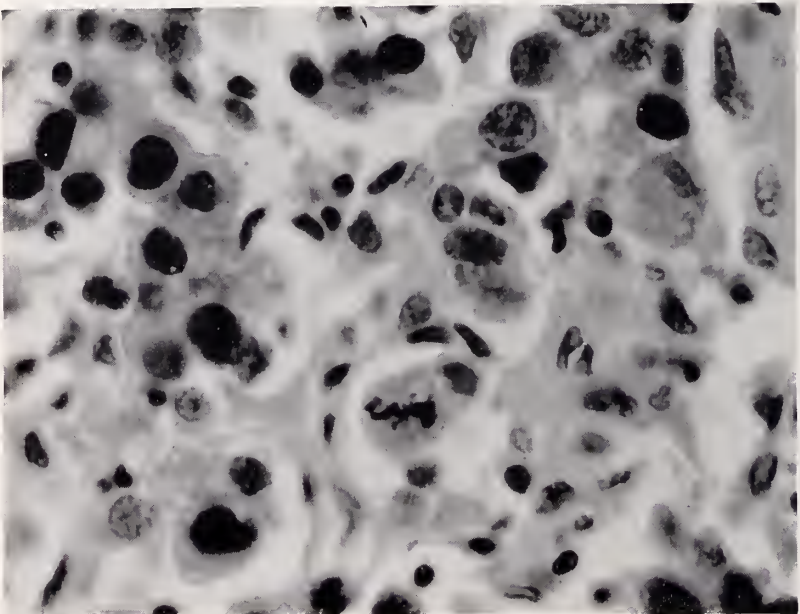


FIG. 4. A section of the posterior lobe of the pituitary shows the tumor cells replacing the usual pituicytes. Mitotic figures are seen. Photomicrograph, hematoxylin and eosin stain, $\times 500$.

Microscopic observations. Sections of the tumor tissue present various patterns. The typical picture is that of large blood sinuses which are invaded by villus-like projections

(fig. 2). The villi are similar to those seen in the chorionic tissue in a gravid uterus. The cell types are of two distinct forms. One type is polygonal in shape and has a large, elongated nucleus with dark cytoplasm; cells of this type form the outer layer of the villi (fig. 3). There are, however, many such cells in all parts of the field with more rounded nuclei or a conglomeration of nuclei. The second type of cell is smaller and cuboidal, having a prominent, round, hyperchromatic nucleus and a pale cytoplasm. These cells, arranged in layers, are found in the villi below the outer layer of cells described above. In some areas these smaller (Langhans) cells are seen to break through the outer cellular layer and are found lying in the blood spaces. They are also found in other areas of the sections. Numerous mitotic figures and giant cells are seen.

Grossly, the pituitary gland has a normal outline, the capsule is intact, and the cellular pattern is essentially normal. On microscopic examination the anterior lobe contains numerous agranular, pale-staining, basophilic cells. The pituicytes of the posterior lobe are almost entirely replaced by tumor cells, particularly of the large nuclear type (fig. 4). Many of these cells show the characteristic syncytial arrangement.

Comment. The characteristic cell elements of a chorionepithelioma consist of the syncytial and Langhans cells, which correspond to the two types found in the case described. The villi invading the blood sinuses are also typical of the pattern seen in chorionic tissue found in the uterus. The Langhans cells invariably break through the outer syncytial layer to invade the blood spaces from which the tumor derives its blood supply (32).

A striking feature in the case is the presence of the characteristic "wandering cell" of the syncytial type in the pars nervosa of the pituitary, although no point of external invasion of the pituitary gland is discernible, nor are such tumor cells found in its anterior lobe.

The discrete, obviously hemic, metastases in the posterior lobe of the pituitary in this case, as in the other mentioned before, warrant some speculation as to the affinity of the pars nervosa for these tumor cells.

It is noteworthy that similar metastases into the posterior lobe of the pituitary has also been seen in cases of carcinomas of the thyroid (11), breast (12, 13), lung (14, 15, 16, 17, 18), pancreas (19), and prostate (20).

A brief review of the blood supply of the posterior lobe of the pituitary shows it to take origin directly from the internal carotid artery via the inferior hypophyseal arteries. The numerous infundibular veins collect the blood, which enters the intercavernous (circular) sinus and drains into the cavernous sinuses (21).

The blood supply of the anterior lobe comes from the internal carotid via the superior hypophyseal arteries. The latter give a direct branch to the anterior lobe. Other branches go to the stalk, where, after an arborization in the substance of the stalk, numerous portal venules emerge and enter the anterior lobe. The blood from there is carried by the lateral venules to the cavernous sinuses.

Thus, the blood supply of the posterior lobe of the pituitary is entirely different from that of the anterior lobe and there is no connection between the respective blood supplies except that both have a common source. This may account for the fact that the tumor cells are not found in the anterior lobe.

Wislocki (22) has further elucidated the method of deposition of tumor cells in the neurohypophysis. He injected colloidal dyes intravenously into living animals and found the dye deposited in the form of *granules* in the tissue spaces

of the pars nervosa. None of these granules was present in any of the tissue fluids of the central nervous system. The colloidal particles are believed to leave the capillaries of the pars nervosa because of the greater permeability of the latter. This permeability may account for the presence of the tumor cells in the posterior lobe but would not explain the significant paucity of the characteristic pituicytes. From the above observation we should expect to find, in most cases of metastatic carcinomas, tumor cells in the neural lobe, particularly in cases where the metastases occur in the brain. This, however, is not so, and it is necessary to look for another explanation. Perhaps this is to be found in the close relationship between the hormones of the pars nervosa and all hormones secreted during pregnancy, including the chorionic gonadotropins.

The chorionic gonadotropins are secreted in high concentration during the first eight weeks of pregnancy, after which they decline and remain steady to the end. Coinciding with the fall in the concentration of the chorionic secretion there begins an increased secretion of pitocin, which reaches its maximum concentration at parturition. Estrone, secreted by the ovaries, follows a similar rising curve and renders the uterus more sensitive to pitocin (23).

It has been shown that pitocin effects vary with the state of the uterus. A gravid uterus reacts more than a non-gravid uterus. It has been found that pitocin has its greatest effect on uterine musculature at the height of pregnancy and that there is no reactivity during involution (24). The pitocin concentration in human blood from males and from pregnant and non-pregnant females is about the same when tested on an isolated rat uterus; but on incubation at 37°C. the blood from the pregnant woman does not produce a contraction, whereas the others do so (25). Cushing (26), discussing basophilic invasion of the neurohypophysis, believed that hypoactivation of the neurohypophysis was the pathological basis of eclampsia.

It is pointed out that in pregnancies where fluid retention produces edema and there is hypertension, all the factors in the blood are normal except for a high titer of hormones (27). The edema, hypertension, and the increased secretion of antidiuretic hormone and pitressin have the same time of onset. The interruption of pregnancy, as is well-known, brings about a dramatic improvement within 24 to 28 hours.

These facts emphasize the close relationship of the hormones of the neurohypophysis to normal and abnormal pregnancy.

There is a definite sequence of events by which the many hormones secreted during pregnancy combine and react to produce a normal pregnancy, parturition and post-parturition. An upset in this hormonal pattern occurs in the toxemias of pregnancy and other abnormal pregnancies, such as abortions.

The change occurring in pregnancy is the simultaneous growth of chorionic tissue and the development of the embryo. The formation of a chorionepithelioma in the uterus may be regarded as an abnormal ending of the post-partum period. Then, the chorionic gonadotropins are found to reach a high concentration instead of falling to a low level.

Chorionic tissue, as mentioned before, consists of trophoblasts and Langhans

cells. The trophoblasts eat their way into the uterine wall and so establish a strong foundation for the developing embryo. The histologic appearance of chorionic tissue during pregnancy might well be mistaken for chorionepithelioma. The factor determining the presence of chorionepitheliomas, which is the continued growth of normal chorionic tissue (28), is the increased secretion of chorionic gonadotropins. The trophoblast normally possesses invasive properties indistinguishable from those characteristic of malignant tissue. The question arises, what restrains the invasiveness of the trophoblast? Novak (29) feels that a lessening of the maternal resistance might be a factor in the development of such a lesion as hydatidiform mole and, on the other hand, that the occasional spontaneous regression of even the malignant trophoblastic neoplasm can be explained by an effective counter-charge of the maternal defense forces. *

That the hormonal secretion may play an important rôle in this defense may well be understood.

Observations on pituitary hormones and the malignancy of the chorionepithelioma. Alcohol-ether extracts of urine from patients with malignant tumors, injected into animals, cause the body weight/spleen and body weight/gonadotropin ratios to drop from 20 to 80 per cent below the same ratios in controls. This constitutes a "biological test" for malignancy. Beard and his co-workers (30) found that 39 out of 40 known cases of malignancy gave a positive test, while all 26 controls were negative. The test is found to be positive also in normal pregnancy and is negative in a hypophysectomized rat. These investigators believe that all malignant urines contain a protein or sterol which stimulates the pituitary to secrete another substance which is responsible for the malignant test. Their observations and conclusions are supported by Gurehot et al (28). It is sufficient to say that a direct relationship exists between the two.

Sittenfield (31) from his review of the experimental and clinical evidence for the role of the pituitary in influencing the growth of malignant tumors, believes that the pituitary exerts a definite influence but that the chain of evidence is incomplete. Whether the neurohypophysis shares this influence is only a matter of conjecture. Separate studies for both lobes of the pituitary have not been carried out. The role of the secretions found in the pars nervosa in the development, growth and subsequent retardations of chorionic tissue has not been investigated.

SUMMARY

1. One case of chorionepithelioma limited to the infundibulum and posterior lobe of the hypophysis is reported. Another case of chorionepithelioma in the right occipital lobe and posterior lobe of the hypophysis is mentioned. In both instances the affected patients were males.

2. An attempt is made to explain the presence of the tumor cells in the posterior lobe of the pituitary and their absence in other parts of the pituitary.

3. Observation on secretions found in the pars nervosa and their rôle in pregnancy are reviewed. The development and growth of chorionic tissue forms an essential constituent of pregnancy. The pituitary hormonal factor influencing

malignant growth is mentioned, and it is suggested that the hormonal secretion found in the pars nervosa may contribute its share to this influence in the growth of the chorionepithelioma.

I wish to record my deep appreciation for the invaluable guidance of Dr. Joseph H. Globus in the preparation of this paper.

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PRODUCTION OF A CONSTANT PLASMA PENICILLIN LEVEL BY MEANS OF DAILY INJECTIONS OF PROCAINE PENICILLIN IN OIL WITH ALUMINUM MONOSTEARATE*

LOUIS E. SCHAEFER, M.D. AND IRA A. RASHKOFF, M.D.

Dosage schedules of penicillin are being modified constantly as more is learned of the use of the drug in various infectious diseases. To meet these changes a variety of preparations have been introduced which make it possible for the physician to provide almost any desired range of penicillin levels with a minimum number of injections.

Up to this time, however, there has been no way of maintaining a constant high level of penicillin in the plasma, except by giving several injections a day, or by using a renal blocking agent such as caronamide or para-aminohippuric acid (1, 2). A single daily injection of crystalline penicillin will produce a measurable level that lasts for about four hours. To maintain a constant therapeutic level with this product, therefore, three to six injections a day are required. A single daily injection of procaine penicillin, on the other hand, will provide a measurable level for 24 hours, but this level falls to the 0.05 to 0.2 unit per c.c. range by 24 hours, and in many cases is less than 0.05 unit (3, 4). Furthermore the daily injections of procaine penicillin do not produce a cumulative effect.

Obviously, a schedule which would provide a penicillin level that never falls below therapeutically adequate range, and yet would require only a single daily injection would be useful in those diseases in which a continuous high level of penicillin is preferable to a discontinuous level, or a constant low level with daily peaks (5, 6, 7, 8).

Because of the fact that procaine penicillin in oil with aluminum monostearate (small particle) produces a therapeutically effective level for at least 72 hours (2, 3, 4), it was thought that a cumulative effect might be obtained by injecting this preparation daily. Kitchen, Thomas and Rein (11) showed this to be the case in nine patients. We tested the same system in 19 control patients who were given 300,000 units intramuscularly each morning for three to six days. The results of this experiment are shown in Table I.

The average penicillin level increases daily from 0.16 unit per c.c. after the first injection to 0.48 unit per c.c. after the fifth injection. At this point the level stabilizes and remains in the 0.5 unit range. In ten of the 16 patients (63%) who received the drug either five or six days, the levels followed the average curve. In the other six patients (37%) the levels did not conform with the average, but in no case did the level ever drop below 0.2 unit per c.c.

It was felt that a dosage schedule of this nature would be useful in a disease such as subacute bacterial endocarditis where long-term treatment is needed, and in which it is believed that successful treatment requires the presence of a constant plasma penicillin level five to ten times greater than the sensitivity of the infecting organism (8, 9, 10).

* From the First Medical Service and the Department of Bacteriology, the Mount Sinai Hospital, New York, New York.

Five patients with subacute bacterial endocarditis have been treated in this fashion. The first of these cases is briefly described.

TABLE I
*300,000 Units of Procaine Penicillin in Oil with Aluminum Monostearate
Injected Daily*

Penicillin Level in Units per c.c. of Plasma

PATIENT	1 DAY	2 DAYS	3 DAYS	4 DAYS	5 DAYS	6 DAYS
H. K.	0.2	0.2	0.66	—	—	—
F. B.	0.2	0.44	0.5	—	—	—
N. B.	0.1	0.2	0.44	0.44	0.5	0.5
S. N.	0.13	0.2	0.4	0.2	0.4	0.44
L. D.	0.2	0.2	0.5	0.5	0.66	0.5
J. T.	0.1	0.2	0.4	0.5	0.4	0.2
R. S.	0.04	0.2	0.4	0.4	—	0.5
M. M.	0.2	0.44	0.4	0.2	0.2	0.8
B. E.	0.2	0.2	0.2	0.66	0.66	0.57
M. R.	0.13	0.2	0.44	0.66	—	0.66
J. G.	0.13	0.13	0.2	0.2	0.2	0.57
J. S.	0.1	0.2	0.5	0.57	0.66	0.57
W. C.	0.07	0.1	0.2	0.57	0.5	0.57
V. C.	0.2	0.4	0.5	0.4	—	—
M. D.	0.13	0.2	0.4	0.2	0.44	0.5
S. L.	0.5	0.66	0.8	0.66	0.5	—
V. C.	0.5	0.2	0.2	0.44	0.4	—
C. R.	0.2	0.2	0.5	0.66	0.66	0.66
W. L.	0.13	0.2	0.2	1.0	0.57	0.2
Average . . .	0.16	0.25	0.35	0.43	0.48	0.51

Levels determined by the tube dilution method with *Staphylococcus Aureus* H.

The penicillin for this study was supplied, in part, by the Upjohn Co., Kalamazoo, Mich.

CASE REPORT

History. B. S., a woman aged 23 years, with evidence of rheumatic mitral stenosis and insufficiency was found to be suffering from subacute bacterial endocarditis due to a hemolytic streptococcus. The organism was sensitive to 0.02 unit of penicillin per c.c. She was given 300,000 units of procaine penicillin in oil with aluminum monostearate twice a day for four days, and then once a day for 39 days. The penicillin level 12 hours after the first dose was 0.66 unit per c.c. On the sixth morning, following five days of therapy, it was 0.8. Thereafter, it remained between 0.4 and 0.8 unit per c.c. for the full course of treatment. The blood culture became sterile and the temperature normal after three days of treatment. The patient is seen once a month in the Follow-Up Clinic, and at the end of six months there was no evidence of recurrence.

Comment. The foregoing case is presented as a clinical demonstration of an experimentally-tested method of obtaining high plasma penicillin levels with a single daily injection of procaine penicillin in oil with aluminum monostearate.

It also demonstrates the value of this observation, as regards the patient's comfort and the ease of treatment, in a disease requiring a prolonged course of therapy.

CONCLUSIONS

1. A constant plasma level of penicillin which is greater than that attained by a single daily dose of any previously investigated preparation may be maintained by the administration of 300,000 units of procaine penicillin in oil with aluminum monostearate every day.

2. This level, after the fifth injection, averaged 0.5 unit per c.c. at all times, and in no individual case did it ever fall below 0.2 unit.

3. A dosage schedule of this type is of value in the long-term treatment of a disease in which the therapeutic objective is the continuous presence of a relatively high concentration of penicillin in the plasma.

4. A case of subacute bacterial endocarditis, successfully treated in this manner, is briefly reported.

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TO-AND-FRO MOTION RANGE AT THE FOURTH AND FIFTH LUMBAR INTERSPACES

STANLEY S. TANZ, M.D.

*(From The Orthopedic Service, Mt. Sinai Hospital, New York,
Dr. Robert K. Lippmann, Chief.)*

Since back motion is greater in the young than in the old, we decided to study in some detail the relation to age of fourth and fifth lumbar interspace ranges of motion.

We felt that once we had established a standard for normal, it would be possible to decide what was abnormal and of diagnostic significance. We hoped that this yardstick would be of value in making indications for and judging results of spine fusion. We also investigated the relationship of low back pain to motion range at these interspaces.

The literature on this subject is scant. In 1931, The Scandinavian Bakke studied spinal motion ranges by X-Ray in 22 normal subjects. Almost all were less than 30 years old, and usually only a portion of the spine was studied. Lumbosacral motion was examined in only 3 subjects over 30, for to-and-fro range, and in only 1 individual over 30, for lateral bending range.

Although Duncan and Horn in 1942 reported that in herniated disk cases, to-and-fro and lateral bending films "... demonstrated a lack of spinal mobility localized to the involved joint ...," in 1944 Knuttson came to the opposite conclusion, namely that excessive and abnormal (tilting and parallel displacement) motion was present at the involved disk site.

In 1946, Hyndman made a similar study comparing normal subjects with subsequently proven disk cases, and made the statement, without elaboration, that he "... was unable to establish an index of change that had sufficient value in differentiating the normal from the abnormal ..."

In 1949, Begg and Falconer mentioned that in normals "... movement is usually greatest at the lumbosacral disk, but alters with the size of this variable disk, while above this level it decreases progressively. ... " They mention limitation of motion in disk cases at the site of herniation in 7 of 10 cases studied, concluding that motion studies preoperatively in disk cases "... therefore is helpful in most cases, but not in all ... " in establishing the diagnosis.

MATERIAL AND METHOD

While the inaccuracy of to-and-fro X-Rays in determining small degrees of motion was appreciated, it was believed that a study, personally supervised with regard to positioning, and with carefully rechecked measurements, was indicated.

The subjects of our investigation were 50 individuals selected at random from our clinic and hospital population, predominantly over 40 years of age (45 of 50 subjects) and excluding any known disk syndromes. Because of the source, back pain of some degree was not uncommon.

Both to-and-fro and lateral bending films of all 50 subjects were taken in

recumbency. Only the to-and-fro X-Rays were used for measuring motion since A-P views were usually not strictly superimposable and since the lateral bending range was small compared with the to-and-fro range. In those cases with no lumbosacral motion on to-and-fro bending, motion was also absent on lateral bending.

We subsequently examined 7 children (aged 18 months to 12 years) for to-and-fro motion to supplement our study.

Although individual variations were large in all groups investigated, it was felt that the conclusions relating to the group over 40 were valid because of the size of the series. (Despite large standard deviations, probable errors were not excessive.) It would be instructive to study a larger number of children, but this was not our primary objective.

Our measurements of motion were made according to the method described by Begg and Falconer.

1. *Relation of Motion Range to Age.* In evaluating the effect of age on motion at the fourth and fifth lumbar interspaces, the average motion range was determined for each decade (Table 1).

TABLE 1
Relation of Age to Average Motion Range (57 subjects)

JOINT	AGE					
	1½-12	20-29	30-39	40-49	50-59	60 and over
L-S	21°	9°	11°	8°	8°	8°
L4-L5	19°	15°	15°	14°	11°	9°
L4-L5-S1	40°	24°	26°	22°	19°	17°

At 18 months, LS motion was 28°, and L4-L5 motion 26°. Although large individual variations were apparent, about a third of the infantile motion range had been lost by the age of twelve years.

Table 1 revealed a gradual and relatively constant decrease in L4-L5 motion for each decade, whereas the decrease in L-S motion range was rapid until the age of twenty, and only very slight thereafter.

2. *Cases With No Detectable Lumbo Sacral Motion.* No lumbosacral motion was detectable by X-Ray in 13 of these 50 adult subjects. No individual under 40 years failed to reveal lumbosacral motion, whereas almost 30% of those over 45 showed no motion by X-Ray, at this level.

There was no significant difference in these 13, as compared to the remaining 37, in respect to the incidence of obesity, sex, or radiologically demonstrable osteoarthritis, (54% and 56% respectively for the last.)

Of these 13 subjects, 6 showed no significant X-Ray abnormality. There were 3 cases with marked lumbosacral narrowing, and 1 case each of sacralized L5 (but no L4-L5 motion); lumbarized S1; very slight L4-L5 spondylolisthesis; and Paget's disease not involving the spine or sacrum.

In all these 13 cases, had spine fusion been performed without preoperative

bending films, post-operative X-Rays would certainly have indicated successful fusion whatever the real surgical degree of success.

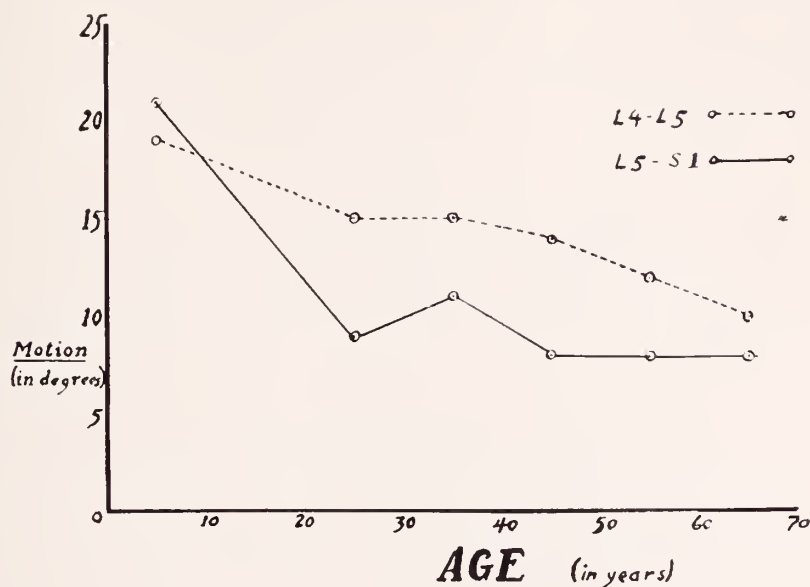


FIG. 1

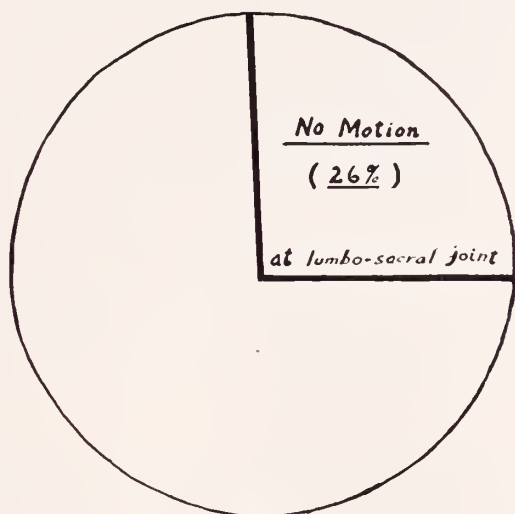


FIG. 2

In this group of 13 cases, L4-L5 motion range was studied, omitting the case with L4-L5 spondylolisthesis. Under 55 years of age (5 subjects), the fourth interspace motion range was found to have increased (average 17°), whereas after 55 years (7 subjects), it was found to have decreased below normal (average 6°).

3. *Relation of Fourth to Fifth Lumbar Interspace Motion Range.* Table 1 suggested that L4-L5 motion was usually greater than L-S motion in adults. Analysis of our series revealed this to be the case in 31 adults (62%) whereas the two joints had equal motion ranges in another 5 adults (10%). In only 14 adults (28%) did lumbosacral motion range exceed the motion at the space above.

4. *Low Back Pain.* The fifth decade (40-49 years) showed a slightly higher incidence of frequent, moderately severe attacks of low back pain, than any other decade.

Low back pain caused no significant difference in the fourth or fifth lumbar interspace motion range (averaging 14° and 8° respectively) compared to the average motion range in pain free subjects of similar ages.

The group showing absence of lumbo sacral motion by X-Ray, had practically the same incidence of low back pain (24%) as did those showing motion radiologically (22%).

DISCUSSION

Since it is not rare to find no detectable lumbosacral motion in subjects over 40 years of age, the employment of preoperative bending films is recommended for patients undergoing spine fusion. Such films should allow for a better evaluation of bending X-Rays taken during convalescence. Of patients showing no motion on post-operative bending films, some had no detectable motion prior to surgery. It has moreover been often observed that many clinical successes do not have fused spines by X-Ray, and preoperative bending X-Rays might reveal that a sufficient motion loss following operation caused the satisfactory result.

In contrast to the recent statement of Begg and Falconer that "... motion is usually greatest at the lumbosacral disk . . ." we found motion at this disk to usually be less than at the interspace above. We therefore cannot subscribe to their theory that when motion at the fifth interspace is less than at the fourth, a herniated disk at the former level should be suspected.

The usually greater motion at the fourth interspace than at the fifth may account for the greater difficulty in attaining surgical fusion at the former.

The decrease of lumbosacral motion with age after 40, is too slight to warrant consideration as a factor in making spine fusion indications, especially since there is no apparent relation between the motion range at the fourth and fifth lumbar interspaces and the incidence of low back pain.

SUMMARY

1. 57 subjects, the great majority over 40 years old, were studied by X-Ray to determine the normal pattern of motion at the fourth and fifth interspaces at various ages in the to-and-fro plane.

2. At any age, large individual variations in motion ranges were apparent. However, on the average, motion at both joints was found to diminish with increasing age. The lumbosacral motion loss occurred largely in youth, whereas the fourth interspace motion loss was more uniform and gradual throughout life.

3. Neither sex, obesity, osteoarthritis, nor low back pain seemed to appreciably influence the range of motion.

4. About one fourth of subjects beyond 40 years of age revealed no lumbosacral motion by X-Ray. This group showed at first a compensatory increase in motion at the interspace above, but with age, this fourth interspace motion range decreased quite rapidly.

5. Motion at the lumbosacral joint was found usually to be less than motion at the fourth interspace.

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LIFE'S LATER YEARS
STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[New York City]

PART XII

THE NINETEENTH CENTURY (CONTINUED)*

In the breathtaking advances of medical science in the second half of the nineteenth century one might well expect to find the study of old age submerged and neglected. Actually the discovery of the role of pathogenic organisms by Pasteur and the application of this knowledge to surgery by Lister brought inestimable benefits to old and young alike, in much the same way as had the first use of volatile anesthetic agents in the eighteen forties and fifties. Nor should we forget that the increasing accuracy of the methods of clinical study led to more refined diagnosis and more effective treatment in internal medicine, and to the extensive development of the specialties of neurology, psychiatry, dermatology, otology and laryngology. In the flood of medical publications resulting from this intensive study of diseases and their causes we find numerous contributions to old age which indicate that in France and Germany particularly, the subject continued to grow in importance with broader understanding of the basic sciences.

The stimulating and productive efforts of French medicine which had in the first years of the century drawn physicians from all over the world to Paris proceeded with undiminished activity. In addition to Pasteur we note such figures as Claude Bernard, Charcot, Brown-Séquard, Flourens, Nélaton, Broca, Huchard, Marie, Duchenne, and Déjerine. Many of these men attained their fame as members of the staffs of the Salpêtrière and the Bicêtre. In the bulletins of the *Société Anatomique* of Paris one finds many reports of aged individuals studied both clinically and pathologically. In the 800 page volume for 1876 there are 63 reports of men and women over 60 years (1). Much of this material is worthy of more careful study but a few cases will be mentioned in detail later. Other sources of material on old age are the doctoral theses written by students but reflecting the views of their teachers, and the encyclopedias of medicine which have in all countries been favored by publishers and writers, and presumably by physicians seeking to catch up on missed reading.

In the supplement to the *Dictionnaire des dictionnaires de médecine* (2), published in 1851, we find the maladies of old age described at length by E. M. Gillette (1800-1859). He differentiated the age of decline, old age proper, and decrepitude, surveying the entire field thoroughly, giving full references to contemporary writers, and describing freely his own experiences at the Salpêtrière.

* This is the twelfth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in the form of a monograph.

The same volume contained an article on "Ages" by Durand-Fardel, of whom more later.

The first edition of Bouchardat's (1806-1866) work on diabetes appeared in 1851 (3). Allen has termed him "the most brilliant clinician in the history of diabetes," and Magnus-Levy emphasized that Bouchardat's advice, "*manger le moins possible*," gave in four words a practical prescription for every case (4). The author discussed the age incidence of the disease and behavior of older diabetics under varying circumstances. In the second edition, published in 1875, this phase of the subject was treated in greater detail.

In 1853 J. H. Reveillé-Parise brought out his large volume on the hygiene of old age, described by Durand-Fardel as a gentle paraphrase of La Rochefoucauld's "*Peu des gens savent être vieux*" (5). The subtitle is highly descriptive: "Researches on the physiologic state, the moral faculties, the diseases of advanced age, on the most certain means, the better tried ones, of sustaining and prolonging the vital activity at that epoch of existence." This is a gracefully written work embodying the best views of the day, but historically has its roots in the hygienic works of the Arab physicians of the Middle Ages.

Marie Jean Pierre Flourens (1799-1867), protégé of Cuvier, was professor of anatomy at the University of Paris, where he carried on fundamental studies of cerebral functions, establishing the vital center in the medulla, the function of the semicircular canals and the relation of the cerebral cortex to vision. His volume on *Human Longevity* depended greatly on the work of Buffon, and set forth the axiom that since it takes a man twenty years to grow, he should live five times that period or one hundred years (6). His views on old age were reminiscent of Bichat.

In 1854 Charles Louis-Maxime Durand-Fardel (1815-1899), who had been trained at the Salpêtrière and the Bicêtre, and practiced at Vichy, published his excellent practical treatise on the diseases of the old. In his preface he states that he "has lived a long time among the aged, has attached himself to their miseries and studied them with a profound interest without knowing only if some day he would have his share." The introduction is devoted to the changes of the aging process itself. The section on the central nervous system occupies 330 pages, the respiratory tract 307 pages, the circulatory system 80 pages, the abdomen including the genito-urinary tract, 116 pages. The appendix devotes 26 pages to gout and 5 pages to the diseases of the skin. The great merit of this work lies in the abundant case reports with postmortem correlations (7). The emphasis on the brain is to be explained by the author's own interest and previous publications (8) as well as the general background of French research. In the heart section we find no mention of the role of the coronary vessels, but excellent descriptions of both cardiac aneurysm and cardiac rupture which is considered a common cause of death in old age. Durand-Fardel in his preface acknowledged his debt to Canstatt, but had the obvious advantage of vast clinical experience over his German colleague. This French work has a sound basis in the actual observations of the author and his colleagues in the great Parisian institutions for the aged.

The importance of these special institutional influences cannot be overemphasized and is seen everywhere in French medical literature on old age. Inglessis, one of Chareot's students, in 1855 presented a thesis on cerebro-spinal meningitis as seen at the Salpêtrière (9). Cruveilhier, pathologist of this great combined hospice and hospital, at a meeting of the Anatomical Society (1856),



FIG. 1. MARIE JEAN-PIERRE FLOURENS (1799-1867)

discussed a case of congenital left sided diaphragmatic hernia in a new-born, and mentioned that he had observed a diaphragmatic hernia, probably congenital, in a woman aged 70 years, the strangulation of which caused death (10). G. S. Empis, physician to the home for female incurables, reported on progressive muscular weakness in the aged, pointing out that general muscular atrophy is associated with discoloration of the tissues and a tendency to vertigo, gastralgia,

precordial oppression and palpitation (11). C. M. E. Potain, well known to Americans as an eponym, contributed two cases of interest in his capacity as physician to the *Hospice des Menages*; one a man of 72 with progressive senile dementia who died of gangrene of the leg, and at autopsy showed ventricular aneurysm with closure of the left recurrent branch of the left coronary artery (12); and the other, a man of 73 who died with painless hepatic enlargement



FIG. 2. CHARLES LOUIS MAXIME DURAND-FARDEL (1815-1899)

and who showed at postmortem section a perforated carcinoma of the stomach with liver metastases and diffuse peritonitis (13).

An extremely important study of tuberculosis in the aged was published from the Salpêtrière by L. Moureton (14), in which the author emphasized that the disease is less rare than generally thought, that it may continue to progress in old age although beginning much earlier, and that it may develop in old people who have had no previous infection. He pointed out how the diagnosis may be

missed in old age because the usual signs are missing in the old. Furthermore, acute tuberculosis, noted heretofore as developing only in youth and adult life, may show up in old age and is not at all rare. The invasiveness of the disease was as marked in old age as in youth.

Regnard's case of senile dementia with subdural hemorrhage (15), Vulpian's study of senile fatty changes in the cerebral vessels of mammals (16), and Maindron's fusiform aneurysms of the terminal aorta with aortic rupture in a woman of 71 years (17), form a background for Marcé's (1828-1864) pathologic studies of senile dementia (18). As psychiatrist at the Bicêtre, he was able to describe some 40 cases, ranging from 50 to 84 years of age and to conclude that the mental changes of old age are not a distinct entity but may be associated with diverse organic affections of the brain, such as apoplexy and cerebral softening. The differentiation from general paralysis was made on clinical and pathologic grounds.

Along similar lines Legrand du Saulle described the position of the aged in relation to the law, the relation of mental states to criminal acts (19). He described physiologic, pathologic and mixed mental states. Age alone was no excuse for misdeeds. He discussed also the sexual transgressions of the senile dement, which at that time were not treated as criminal acts if the physician's opinion substantiated the diagnosis of mental disease.

Gosselin (1815-1887) in his surgical lectures stressed the influence of age upon the prognosis of surgical diseases and the consequence of operations (20). He believed that strangulated hernia may be operated at any age with equal chances of success (21). A. A. S. Verneuil (1823-1895) another distinguished Paris surgeon, discussed surgery in the aged and explained that bad results were due to acquired diseases rather than to years themselves. Not all the old are sick but precocious senility occurs in alcoholism, malaria and other intoxications (22). Dodeuil's studies on the pathology and symptomatology of prostatic disease comprised a treatise of 110 pages and yielded evidence of the surgical thinking of that time (23). In the same field A. Dieu studied the sperm of old men, reporting on the findings in 105 cases, ranging in age from 64 to 97 years, and stressing the medico-legal significance (24). Douaud, a student of Vulpian, published a thesis on the fatty degeneration of the muscles in old age (25).

The bright star of the Salpêtrière staff was for many years the brilliant neurologist, Jean Martin Charcot (1825-1893). A fascinating lecturer and stimulating thinker, he attracted large numbers of foreign physicians to his clinics at the old hospital. Thanks to translations by an Englishman and an American, his *Clinical Lectures on the Maladies of Old Age* (1867) have attained a reputation far beyond their actual worth, since of 22 lectures only three are devoted to old age, the others being concerned with gout and rheumatism, acute and chronic (26). The work does not purport to cover the entire field and cannot be compared with Durand-Fardel's masterpiece. Nevertheless the language of Charcot is so vivid even in translation that his work is eminently readable and entertaining as well as full of sound observation.

In describing the clinical picture of disease in old age, he stressed the unique

character of the patients to be studied in the vast female population of the Salpêtrière. A brief historical review highlighted French contributions to the subject, although he paid his respects to Canstatt, Geist and Mettenheimer as representatives of "science beyond the Rhine." In his opinion "most of the medical works of the past century which touch, in a special manner, upon the senile period of life . . . are more or less ingenious paraphrases of the famous treatise *De Senectute* of the Roman orator." He recognized certain special diseases of old age, such as senile marasmus, senile osteomalacia, senile atrophy of the brain and arterial atheroma. Other diseases seen in all periods of life have special characteristics in the aged. Finally he explained the occurrence and the behavior of infections in the old, pointing out the observations of his student Inglessis on meningitis (9) and of Vulpian's student Moureton on tuberculosis (14), and concluded with the rhetorical question that neatly tied up the whole subject for a Frenchman.

"And who besides, does not know that Louis XV died of smallpox at the age of sixty-five?"

Pierre-Adolphe Piorry (1794-1879) is justly famed as the inventor of the pleximeter and the pioneer of mediate percussion in his relatively youthful days. When advanced in years, he held conferences on old age which were recorded by one of his students. He emphasized that the time to combat old age is in youth and deprecated the use of medicines. His conclusions are reminiscent of the wisdom of old men since the beginning of time (27).

"Guard the activity of your spirit, the health of your body, the purity of your conscience, and your old age will be sweet, and death will be unable to frighten you."

Another example of an old physician writing about advanced age from personal experience is the contribution of Diday (1812-1894), the celebrated syphilologist, on senile disturbances of equilibrium (28), in which he discussed his own sensations six years after retirement. Here occurs, apparently for the first time, an epigram frequently quoted by later writers which sounds far better in French than in translation. Whether this was original with the writer is not known.

"Pour la jeunesse vouloir, c'est pouvoir; pour la vieillesse, trop souvent, vouloir c'est douloir."

A contribution by Ferré on the often discussed symmetrical atrophy of the parietal bones of the skull in old age is of interest since it is based on the study of four skulls from the Salpêtrière, from women whose ages ranged from 79 to 88 years (29). In Ballet's contribution to the study of the senile kidney from the Salpêtrière, we find an excellent historical review of previous studies of the kidney in older individuals, emphasizing that the term "senile kidney" should no longer be used to designate a particular state of kidney peculiar to old age (30). The term is not to be taken in an anatomic sense but utilized in relation to cause in order to designate the interstitial nephritis with vascular sclerosis found in old people, just as in adults resulting from lead poisoning or gout. In Martin's study of visceral lesions due to arteriosclerosis we find this opinion confirmed (31). A. F. Voisin published in 1876 his *Clinical Lectures on Mental and Nervous*

Disorders given at the Salpêtrière, in which an excellent discussion of psychosis due to cerebral arteriosclerosis is found with particular emphasis on relation between symptoms and pathological lesions (32).

While Parisian physicians busied themselves in the study of old age, similar activities went on in Nancy, Montpellier and Marseille. In the medical journal of Marseille for 1878 we find several studies on old age from the anatomical and physiological points of view by J. Roux of Brignoles, one of the editors of the journal (33). Other papers treated of traumatic disorders and surgical conditions of the aged. These are well written reviews of current teachings containing little original material. Brousse, chief of the medical clinic at Montpellier, in a monograph on senile involution discussed the theories of senescence, and described the functional and organic changes of old age, concluding that senile involution, like death, is the result of living and is due to general and progressive weakening of the nutrition of the tissues (34).

In 1886 Emile Demange (1846-1904) of Nancy published a small volume of clinical and pathological studies on old age, based on his experience at the Hospice St. Julien where he had observed 500 necropsies (35). This remarkable work is really a study of the physiology and pathology of the senium, with only scant reference to symptomatology and therapy. It is well written with an excellent bibliography and based on the careful observations of a medical man who had already made contributions to the literature on obesity, diabetes, paraplegia, the senile kidney, senile osteomalacia and paralysis (36). The physician of today will feel a strong bond of fellowship on reading his preface in which he thanks "our eminent dean, M. Tourdes (37), in whom I have constantly found a strong support in the midst of the difficulties involved in setting up a clinical service in a home for the aged."

He was particularly interested in arteriosclerosis and believed that atheroma was due to obliterating endarteritis of the vasa vasorum. He stated that this endoperiarteritis was due to stress and strain and was the principal cause of the lesions of old age. His views on the relation of the coronary vessels to heart disease in the aged are likewise amazingly modern and are based on his personal technique of dissecting the finer branches of the coronaries. He found atheromatous changes in the coronaries of 22 out of 23 cases of old people who were not gouty, alcoholic, rheumatic or poisoned by lead, who died of pneumonia, erysipelas, diarrhea, brain hemorrhage or softening, or senile cachexia.

"Up to now the close relations which unite the arteritic lesions of the coronaries to senility have not been sufficiently placed in relief; one has especially sought to explain certain maladies of the heart by lesions of these vessels; thus one has shown that fatty degeneration of the heart is related to atheroma of the coronaries; one knows infarction of the ventricular wall, recognizing as cause an obliteration of these vessels, and leading to degeneration and sometimes rupture of the heart; finally certain varieties of angina pectoris seem to be due to atheromatous alterations of the vessels." This represents an unusually clear conception of the role of the coronaries at a time when the views of most physicians in Europe and the United States were in a state of hopeless confusion. No reference to Demange's original observa-

tions is to be found in any of the histories of cardiology consulted. Huchard does not mention Demange nor does Demange list Huchard in his bibliography. In Cowdry's *Arteriosclerosis* Cobb and Blain quote Magliulo's review of the literature in which Demange's views on spinal cord arteriosclerosis are mentioned (38). The neglect of Demange's careful studies by contemporary and subsequent writers is to be explained in part by his location in a provincial city, in part by his differing from the prevailing view that angina pectoris was a nervous disorder, and finally by grouping him with Jenner, Parry and Hunter whose sound observations on the same subject were also disregarded by other physicians. Among contemporary writers on the heart that Demange quoted were Debove and Letulle (39), his own student, Haushalter (40), Robin and Jubel-Renoy (41), and Peter (42). In Romme's review of the senile heart we find Demange quoted as an authority on old age, and Haushalter's paper repeatedly referred to (43).

The turbulent life of Charles-Edward Brown-Séquard (1817-1894) had included professorships in the United States as well as in France, and had seen a great reputation securely founded on physiological research which had demonstrated the vasomotor nerves and the effects of transection of the spinal cord. At the age of 72 he undertook with the assistance of D'Arsonval to try out on himself the rejuvenating effect of extracts of animal testicles. He reported dramatically on the beneficial effects of the preparation before the *Société de Biologie*, June 1, 1889 (44). For a detailed account of his experiments and their startling effect on the world the reader is referred to Dunbar's contemporary account and to Olmstead's excellent life (45). The remedy was tried out in every kind of hopeless case with reported benefit. "Before the end of the year more than twelve thousand physicians were administering the extract to their patients" (46). In a few years the furore died down, but the ideas of Brown-Séquard laid the foundation for modern endocrine therapy and stimulated the scientific study of the ductless glands. His testicular extract was science's latest answer to the folk-dream of an elixir of life.

In spite of the excitement caused by the demand for the panacea, physicians continued to treat old people according to established principles and from time to time recorded their results. Blum's study of surgery in the aged could be republished under a current date line. In reporting a series of successful operations, he laid emphasis on the preparation of the patient, avoidance of general anesthesia, keeping patient and operating room warm, minimizing loss of blood, rigid antisepsis, liberal feeding and early rising. In his opinion the success of an operation depended less on the age of the patient than on the previous state of health (47). The work of the great French masters of genito-urinary surgery, Felix Guyon (1831-1920) and Joaquín Albarran (1860-1912) contributed to growing understanding of disorders of the bladder and prostate.

In 1895 Jules Boy-Teissier (1858-1908) of Marseille, physician to the Hôpital St. Marguerite, a home for the aged, published his *Lectures on the Diseases of the Aged, given at the Marseille medical school* (48). This work by a clinician trained in the care of the aged is in the modern spirit and well deserves extended com-

ment. He insisted on the study of old age from the biologic as well as the clinical and therapeutic viewpoints. Old age is not a sickness but a natural phase of life. The physician needs to know the period of senescence, by which one arrives at old age and not occupy himself with the already achieved senile involution. He criticized authors who have tried to explain old age by one lesion. He stressed the "coefficient of vital resistance," as being reduced with advancing years and depressed by secondary causes such as acute and chronic infections, intoxications and other acquired morbid states. The reaction against disease in the aged is



FIG. 3. JULES BOY-TEISSIER (1858-1908)

produced in the same way as in the adult, but is as much enfeebled as the coefficient of vital resistance is diminished.

Georges Marinesco (1863-1938) of Rumania (49), trained in Paris, collaborated with P. O. Blocq (1860-1896) in the first description of the brain lesions described later by Redlich as "miliary necroses" (50) and by Simchowicz as "senile plaques" (51). For an excellent discussion and historical bibliography of this important cerebral tissue change, the reader is referred to Critchley's thorough paper on the subject (52).

Magnus-Levy has called the second half of the nineteenth century the heroic age of German medicine and of the other sciences as well (53). The justification for this opinion is seen at once in the names of the leaders, Virchow, Helmholtz,

Bunsen, Gegenbaur, Waldeyer, Du Bois-Reymond, Ludwig, Erb, Billroth, Fraenkel, Cohnheim, Müller and Naunyn. Here as in France the rapid strides in the study and treatment of infectious diseases, in public health methods, and in basic anatomical and physiological concepts led to widereaching benefits for all segments of the population.

With the exception of Uhle's paper on typhoid fever in older people (54), the first important contribution to the subject after Canstatt was the *Klinik der Greisenkrankheiten* of Lorenz Geist published in 1860 (55). The author was a well trained clinician who had published careful studies on industrial phosphorus poisoning (56), and who had worked for 12 years at the Hospital of the Holy Gost, a sectarian institution for the aged in Nürnberg. The book is not only abundantly illustrated by case reports and postmortem findings, but contains many original findings based on Geist's chemical and physiological studies of metabolic processes. Spirometric measurement of the lung capacity based on Hutchinson (57) and analysis of the expired air for carbon dioxide are among the answers Geist was able to give to questions originally asked by Canstatt.

"If I may summarize the status of the metabolism and intermediary metabolism, it appears from these findings that the age involution of the human body does not begin in one organ, and from this spread to the others. The involution which we recognized as an alteration of metabolism is simultaneous and general, the lungs being the organs in which the progressive involution of life can be measured by the products of their physiological activity. In the same relationship as the respiratory capacity diminishes, the changing metabolism will have manifested an increase of nitrogen excretion and a compensating retention of carbohydrates. Thereby intake and output, as long as relative health exists, are equalized but the metabolism in general diminishes from decade to decade."

Although a careful pathologist and trained by 500 autopsies on aged people, Geist showed the prevailing lack of understanding of the importance of the coronary arteries. In discussing stenocardia he states that this condition is combined with pathological conditions of the heart but that it would be erroneous to conclude from it a causal relationship. He quoted Virchow to the effect that only coronary emboli are able by themselves to cause acute paralysis of the heart, the severest form of angina. Geist's work is based on complete knowledge of German, French and English literature and ranks with Fischer, Canstatt and Durand-Fardel as a classical contribution.

Further studies of old age were made at the same time in Frankfurt a/M by Carl Friedrich Christian von Mettenheimer (1824-1898) who worked at the local home for the aged. In his *Sectiones Longaeorum* he has collected, translated and annotated reports of postmortem examinations of centenarians (58). In all he recorded seven cases, namely, Parr, reported by Harvey, Keill's John Bayles, J. H. Vopper reported by Scheuchzer, Haller's 100 year old woman, Poupert's 100 year old woman and Cheselden's two cases. His interest in pathological anatomy is reflected in his more ambitious work on nosologic and anatomic contributions to the study of the diseases of old age, in which are collected case reports and autopsy findings from the Frankfurt Home (59). He attempted to clarify

thereby the whole picture of disease in old age. Although he became personal physician to the Archduke of Mecklenburg-Schwerin and was otherwise busily engaged, he continued to write on the subject from time to time. He was in close



L. M. Geist.

FIG. 4. LORENZ GEIST (1807-1867)

touch with Geist but their plans to bring out a medical journal devoted to the problems of old age were terminated by Geist's death in 1867. Shortly after Mettenheimer's death in 1898 there appeared his *Viaticum*, made up of the experiences and counsels of an old physician for his son on his entry into practice

(60). Many years later (1940) the son published a large volume in tribute to his father called *The Development, Aims and Achievements of an Old Physician* (61). This is a rich source of biographical material not only on Mettenheimer but also on his contemporaries.

Two further studies in the pathologic anatomy of old age came from homes in Vienna. Chrastina reporting necropsies from the home at Alserbach laid stress on findings in so-called senile marasmus, describing tissue and vascular changes.



FIG. 5. CARL FRIEDRICH CHRISTIAN VON METTENHEIMER (1824-1898)

He also stressed organizing and unresolved pneumonia, denying that he had ever seen asthma of nervous origin (62). Engel reported on 500 postmortem sections in men and women of 60 years of age and over. He emphasized that while the home in Währingergasse admitted only poor infirm old people, the majority of the group suffered not only from the predisposition to illness that old age brings but also from certain definite diseases, often multiple. He referred to some individuals as being veritable storehouses of the most varied morbid processes. In

concluding his statistical findings he stated that "the fragility of advanced age consists not so much in lessened resistance to external influences as in the presence of actual disease which is often enough together with minor external disturbances, to bring about death" (63).

In addition to Arnold's study of the cornea and the arcus senilis (64), we find two papers on the mental disorders of old age. Wille's paper was practical and full of clinical understanding (65). He warned of the danger of suicide in the milder cases. Some patients go downhill rapidly but others may last three to four years. Mental symptoms often follow a stroke. He described the nursing difficulties and emphasized cleanliness in order to prevent bedsores. Güntz stressed the need for careful differentiation of senile dementia from melancholia and mania (66). He described eight female patients. In one the mental state followed a stroke; in the others, after the death of their husbands. All were in reasonably good health. He told of one patient who entertained him with tales of Goethe and Schiller at the Weimar court 50 years previously but could not remember the examiner's name. These patients also suffered from mistrustfulness, and persecution manias, and frequently used foul language.

Beneke, distinguished pathologic anatomist of Marburg, contributed in 1879 an essay on age disposition as a contribution to the physiology and pathology of the various age levels of human beings (67). He emphasized the need for more anthropometric studies of the various anatomical systems at various periods in life. This is important since at different life periods the human machine possesses different constitutions, and on these differences indubitably depends the variation in vital manifestations. These changes occur as the necessary consequence of lawfully regulated developmental processes, of the work unavoidably demanded of separate parts of the machine and of the deterioration gradually brought on by work. He adduced abundant statistical material, some of it from reports of the New York City Health Department. He devoted considerable attention to the disposition to disease at various ages. He was certain that continuation of his work would ultimately bring pathologic anatomy and physiology together.

In the lectures of Julius Cohnheim (1839-1884) on general pathology we find a clear statement of his views on the nature of the aging process. He discussed age changes in the elasticity of arteries and ascribed senile atrophy to the effect of disease on tissues and cells combined with other changes which because of their frequency he considered physiological (68). Cohnheim further deserves attention for his experimental study of the effect of ligation of the coronary arteries leading to the erroneous conclusion that the coronaries are end-arteries, occlusion of which always caused death.

The papers of the distinguished neurologist P. J. Möbius on the pupillary reactions (69) and the knee jerk (70) in old age are of genuine clinical importance. He reported that narrowing of the pupils begins at an early age and ends with the pinpoint of the aged. Wide pupils over 50 years suggest a brain lesion. Of 83 patients examined, 60 were over 80 years. Of these 19 had extreme meiosis, 59 moderate; 5 with mydriasis were also blind due to cataract. In studying the

knee jerk he found that weak or absent jerks occur in more decrepit individuals. He believed that this weakening is part of the aging process, and of no practical interest as one does not suspect tabes in 80 year old people. On the other hand it may appear prematurely as other senile changes do. In such a case this finding may substantiate a diagnosis of premature senility in the presence of other changes.

Seidel's work on the pathogenesis, complications and treatment of the diseases of old age appeared in Berlin in 1889 and one year later was translated and pub-



FIG. 6. ADOLF MAGNUS-LEVY (1865)

lished in New York, the first European work on old age to appear in the United States since that of Charcot (71). This is a sound review of existing knowledge presenting no original viewpoints but valuable for its excellent bibliography, and noteworthy for bringing European thinking to the attention of American physicians. Far more important than a book about old age was the actual accomplishment of Max Nitze (1848-1906) who developed the cystoscope in 1879, perfected it in 1886 with the addition of Edison's incandescent lamp and thereby laid the foundation for modern urology and its successful treatment of prostatic hypertrophy, bladder tumors, and calculous disease, in the aged.

Pflüger, the famous physiologist of Bonn (1829-1910), delivered an address in honor of the birthday of Kaiser Wilhelm II, January 27, 1890, on the topic, *The Art of Lengthening Human Life*. This is a good general review of the knowledge to the day, emphasizing the biological nature of death but still clinging to the old beliefs about the longevity of Parr and the others (72).

In 1899 Magnus-Levy established the fall of the basal metabolism with advancing age. In 1941 he, at that time 76 years of age, compared his own basal metabolism during the course of 50 years, showing a diminution in oxygen consumption of 24 per cent (73). In the same paper he quoted the basal metabolism figures of five other well known nutrition authorities in youth and age.

(To be continued)

Robert T. Frank

May 11, 1875–October 15, 1949

It is with a sad heart that I am discharging the painful duty of reporting the death of Dr. Robert T. Frank, which occurred on October 15, 1949. And it is with deep reverence for our departed colleague and my erstwhile chief and friend that I am about to record the many and great accomplishments that have marked his crowded and distinguished life. Some of these, if not all, have left their imprint on the progress of gynecology and medicine in general.

Dr. Frank was born in the City of New York on May 11, 1875. His preparation for his medical career was most painstaking. It was in part provided by the Sach's Collegiate Institute, a school renowned in its day for the thorough training it gave to its pupils, many of whom have left their foot steps in many walks of life. As was the case with a large number of his schoolmates he completed his preprofessional education at Harvard College, receiving the degree of Bachelor of Arts in 1896. This brought him nearer the threshold of his goal as he entered the College of Physicians and Surgeons of Columbia University. Here his ever serious application to his studies was rewarded in 1900, almost a half a century ago, by two degrees, an M.A. and an M.D. With complete disregard for time and effort he spent $3\frac{1}{2}$ years as intern at The Mount Sinai Hospital acquiring his early but sound experience, which stood him well in his subsequent years of distinguished practice in his chosen field.

Perfectionist in his make up he felt the need of further preparation for his life work and had satisfied this urge by a period of study in Europe under the guidance of the master in the realm of pathology. On his return to New York, the practical utilization of this wealth of knowledge was made possible by his appointment as aidjunct in Gynecology at The Mount Sinai Hospital and as a fellow in the Crocker Institute of Cancer Research.

Such was the beginning of a long period of his highly productive activity in the interrelated fields of endocrinology, pathology and gynecologic survey. He was first to demonstrate the female sex hormones in the follicular fluid of the ovary and the circulating blood and first to develop the test, bearing now his name, to identify the estrogens in the circulating blood. As early as 1907, he identified and determined by injecting placental extracts into laboratory animal the presence of estrogens in the placenta. His treatise on the function of the ovaries published in 1911, is still considered a classic. All this placed him among the pioneers in the study of endocrine functions of the placenta, ovary and pituitary gland.

During World War 1, Dr. Frank served as a Captain and Major respectively, with the Mount Sinai Unit, Base Hospital Number 3, in France. On his discharge from the army he had to abandon his work for a time as he moved to Colorado because of an illness he contracted during military service. While convalescing he wrote a text book on Gynecological and Obstetrical Pathology. Upon his full

recovery he returned to the practice of Gynecology remaining in Denver where he was appointed Associate Professor of Gynecology at the University of Colorado, and Attending Gynecologist in the Denver General Hospital. Here, in collaboration with his wife, Rose-Marie Frank, he continued his investigations in Endocrinology.



In 1925 he was recalled to Mount Sinai Hospital as Attending Gynecologist to succeed the late Dr. Joseph Brettauer. There he established the Endocrinological Research Laboratory, and almost succeeded in isolating Alpha-Estradiol in a pure form, when Doisey and his collaborators reported this difficult extraction. Dr. Frank also developed a chick-comb test for the bioassay of Androgens and a rapid rat test for the diagnosis of pregnancy.

In spite of his intensive activity in the field of Endocrinology and a very active

practice, he made many contributions to Gynecologic operative procedures, particularly in the popularization of a modified Manchester operation for uterine prolapse.

His published manuscripts numbered over two hundred. In addition to his book: *Gynecology and Obstetrical Pathology*, he was the author of a book on Female Sex Hormones, and contributor of monographs to Nelson's, Davis' and Prior's compilations in Surgery and Gynecology.

He was a member of many medical organizations; among them the American Gynecological Society, The American Board of Obstetrics and Gynecology, the New York Academy of Medicine, the American College of Surgeons, the Chicago Gynecological Society, Sigma Xi and the Sociedad de Obstetricia y Gynecologia of Buenos Aires.

Dr. Frank, despite his deep interest in the scientific aspect of medicine never allowed it to interfere with his great devotion to his patients, who, as all of us who knew him well, admired and respected him for his rare qualities. Their faith in his skill, dependability, and deep sympathy in their problems of health or otherwise was unshakable. His modesty and humility were well known to all of us. Those of us who were closest to him will never forget his warmth, his kindness, and his patience with the younger men. Always ready to listen and advise, and though he was very critical of others, he was always most critical of himself.

In Dr. Frank's passing we have lost a potent investigator, a great teacher, and above all, a man of sterling qualities.

M. A. Goldberger, M.D.

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Hyperimmune Serums in Treatment of Whooping Cough. J. L. KOHN, et al. Am. J. Dis. Child., 73: 321, September, 1947.

In a previous article on the treatment of infants with whooping cough the importance of good nursing care, oxygen therapy and pharyngeal and tracheal aspiration was stressed. In addition to the above treatment, 151 children were given human hyperimmune whooping cough serum. Of these, 49 received a lyophilized preparation and 109 received a concentrated globulin fraction prepared from hyperimmune serum. Seventy-nine of the children were under 1 year of age. An additional 49 children received refined hyperimmune rabbit serum which also contained a pertussis endotoxoid. Only 2 of these latter children were under 1 year of age. Forty-four per cent of the children receiving serum had evidence of pneumonic infiltration. The serums were given intramuscularly every other day for 3 doses, or, in desperately ill cases, on 3 successive days. Lyophilized serum representing 20 cc. of the original serum was dissolved in 10 cc. of sterile water. The dose of concentrated human globulin was 2.5 cc., extracted from 20 cc. of the original serum. The dose of refined rabbit serum was 10 cc. Of the infants under 1 year who received human serum 70 of the 79 were improved. The apparent response to serum in patients over 1 year of age was not so striking as in the younger group. The improvement noted was a decrease in number of paroxysms and in vomiting. In some patients the improvement was only temporary and it was thought necessary to give additional injections of serum after 5 or 6 days. In the group receiving rabbit serum, improvement was seen infrequently. There were 4 deaths. All these children had received human serum. Only 1 death occurred among the 81 children under 1 year of age. The disappearance of *Hemophilus pertussis* from the nasopharynx bore no relation to the clinical course of the illness and was not influenced by the serum. In many instances, the culture was still positive 4 weeks after the appearance of the whoop. In the children here reported, a skin test with pertussis endotoxin was made before and 3 weeks after the injection of hyperimmune serum. The results were believed to be inconclusive. The therapeutic response was equally good with the concentrated human globulin and lyophilized human serum. It is recommended that one or the other should be given to all infants seriously ill with whooping cough.

The Current Clinical Status of Hepatic Insufficiency. S. S. LICHTMAN. New York Med., 3: 18, September, 1947.

Liver disease is more prevalent than hitherto suspected. Jaundice may appear late or not at all. Clinical awareness of the symptom complex of hepatic insufficiency in its broadest sense is essential for early diagnosis and treatment. At this point the disease may be checked and irreversible changes prevented. With knowledge of the symptoms and signs of hepatic failure at hand and of suitable tests for confirming this diagnosis, the routine clinical investigation of this organ is indicated. The proper selection of liver function tests is guided by the type and grade of liver failure and depends on which of the chief

anatomic systems of the liver is involved, the parenchyma, the vasculature, the biliary tract, or the reticuloendothelial system, and the degree of such involvement. The functional status of the liver is determinable whenever there is the slightest suspicion that it is contributory to the clinical picture. In borderline hepatic insufficiency, *compensated* and *decompensated* phases may be differentiated with the aid of serial liver function tests, liver biopsy and functional response to exercise and intensive therapy. At times the symptoms and signs of hepatic failure are closely simulated in patients with psychoneurotic and "effort syndrome" patterns. Liver insufficiency may be *primarily* hepatic, *secondary* to disease of the heart, thyroid, colon, etc., or *associated* with disease of the brain or kidney.

Diagnostic Procedures in the Investigation of Sterility in the Female; Evaluation of Their Clinical Importance. I. C. RUBIN. Bull. New York Acad. Med., 23: 519, September, 1947.

A minimum investigation of the sterile woman has been outlined by Rubin. It consists of: (1) a good medical and gynecological history, (2) careful general and local physical examination, (3) BMR and other general laboratory blood and urinary examinations, (4) Huhner test and examination of the unmixed specimen of semen, (5) Kymographic Uterotubal Insufflation supplemented when necessary by Hysterosalpingography, (6) basal temperature recording. The essential practical data may be derived from these six steps in the investigation. The others are difficult to carry out or have as yet doubtful practical value. As in all branches of clinical medicine one must in the last analysis exercise clinical judgment in appraising the underlying causes or factors at the basis of the abnormal condition which in the topic under present discussion is genetic failure. Routinization has not led to more favorable results than judicious selection of the practical measures at our disposal.

Preliminary Report. The Inhibition of Erythema Solare in the Normal Subject with Pyribenzamine. A. KURTIN, W. BIERMAN AND R. YONTEF. J. Investigative Dermat., 9: 163, October, 1947.

It has been demonstrated that iontophoresis with pyribenzamine will inhibit erythematous response to ultraviolet radiation. The histamine mechanism of sunburn is discussed.

Carcinoma Involving the Common Bile Duct. H. E. LEITER. Surgery, 22: 627, October, 1947.

Four cases were presented in which carcinoma involved the common bile duct. In two patients a one stage duodeno-pancreatectomy was done while in the others the lesion was so situated that a segmental resection could be carried out. All 4 cases survived operation. The historical features, incidence, and pathology of choledochal neoplasms were reviewed. The discussion included some of the problems of operative technic and post-operative cholangitis.

Extrinsic Lesions Affecting the Recto-sigmoid. R. H. MARSHAK. Am. J. Roentgenol., 58: 439, October, 1947.

There are many pathological processes arising in the pelvis exclusive of the large bowel which, because of their proximity produce defects in the recto-sigmoid. This report deals with the appearance of the bowel at the barium enema examination of such cases. An example of a lesion which can produce extrinsic pressure is endometriosis. This lesion may extend to the bowel and produce symptoms of intestinal obstruction similar to cancer in the same area. Likewise, other lesions arising especially in the uterus, tubes, and ovaries may produce the same sequence of events. In some cases the deformity of the recto-sigmoid is typical, whereas in other instances a differential diagnosis from cancer of the bowel is impossible. Usually, in the inflammatory cases, the mucous membrane is intact whereas in the neoplasms arising outside of the bowel the appearance of the edges of the

defects is important as here the mucous membrane also may be destroyed as in an intrinsic carcinoma. The problem is significant in the proper evaluation of masses in the pelvis. The cases fall in the following groups: 1. Endometriosis, 2. Carcinoma of the cervix with a frozen pelvis, 3. Chronic inflammatory disease, 4. Ovarian carcinoma and ovarian cysts, 5. Effects of radiation therapy, 6. Fibroid uterus, 7. Sigmoiditis, 8. Lymphosarcoma and metastatic carcinoma, 9. Retroperitoneal tumors, 10. Post-operative adhesions.

Immunologic Relationships of the Antibiotics and Trichophytin. Clinical Observations and Animal Experiments. S. M. PECK AND S. SIEGAL. J. Investigative Dermat., 9: 165, October, 1947.

It was possible to sensitize 4 of 9 guinea pigs with penicillin, amorphous and crystalline, as demonstrated by a positive Dale test. The Arthus phenomenon could not be elicited with crystalline penicillin on repeated intradermal injections in rabbits. Penicillin was inactive in the Shwartzman phenomenon, either as the preparatory or eliciting factor. The high mortality of guinea pigs after repeated injections of small amounts of penicillin, whether amorphous or crystalline, was noted. It was not possible to sensitize guinea pigs with streptomycin, the isolated uterine strip being used as the test object. However, streptomycin-injected animals showed positive uterine strip contractions to penicillin and trichophytin, suggesting the presence of some common antigen. Repeated subcutaneous injections of streptomycin failed to elicit the Arthus phenomenon in rabbits. However, in two animals following such treatment the Shwartzman phenomenon was induced, suggesting the presence of circulating anti-streptomycin antibodies. Numerous clinical observations support the concept that two forms of penicillin sensitivity are based upon previous fungus disease of the skin. One of these is the latent, "spontaneous" type, where there is a positive 48 hour skin test to crystalline penicillin, but no other manifestations. The second form, presumably activated from the latent type by penicillin treatment, is characterized by the erythematous-vesicular or "id-like" eruption. Penicillin and trichophytin are seen to possess distinct chemical and biologic characteristics. They are separate substances and the allergic responses to them, while associated, are likewise distinct, and indicate their independent antigenic activity.

A Physiologic Approach to Cardiovascular Roentgenology. M. L. SUSSMAN. Minnesota Med., 30: 1041, October, 1947.

The author briefly touches on some of the phases of cardiac roentgenology which have interested him. He selects for presentation particularly those facets of cardiovascular physiology in which the roentgen ray can play an important role. It is his intention to provoke consideration of these thoughts: It is no longer necessary for roentgenology to confine itself to a questionable static analysis of cardiac topography. The roentgenologist has a tool which is particularly suited to a physiological approach to cardiac dynamics. However, his participation in a team will permit an integrated study which cannot be achieved by one individual alone. Newer techniques permit the study of the individual and his cardiac function. This is the fundamental development in clinical physiology. Reliance on prototypes in the postmortem room or on the experimental animal has become less necessary than heretofore.

A Simple Method for the Determination of Salicylates in Blood. M. VOLTERRA AND M. D. JACOBS. J. Lab. & Clin. Med., 32: 1282, October, 1947.

A method based on the xanthoprotein reaction is described for the determination of salicylates in blood. This technique is both rapid and simple and may be carried out very accurately with either a photoelectric or a visual colorimeter. It may also be employed for direct comparison with known dilutions of potassium dichromate. The results compare very favorably with those of Coburn. Unlike that method, it does not require the preparation of a standard for each determination, when using the photoelectric colorimeter.

Submucous Lipoma of Transverse Colon with Intussusception. A. DALLOS. *Am. J. Digest. Dis.*, 14: 345, November, 1947.

One case of a submucous simple lipoma of the transverse colon with obstruction and intussusception is reported. The purpose of the demonstration is to remind the diagnostician, as well as the surgeon, that among the tumors of the intestinal tract are benign simple lipomata, which can be treated with simple excision and primary repair of the bowel. Lipomata may occur anywhere in the alimentary tract. They may never produce symptoms. Those which produce symptoms show mostly the clinical picture of a chronic intestinal obstruction. The other clinical picture may be that of an acute intestinal obstruction mostly caused by an intussusception. In most cases in the literature, resections in one or two stages were performed although a simple excision could have been performed. With the advancement of x-ray studies, it should be possible to make the diagnosis preoperatively more frequently.

New Approach to the Treatment of Esophageal Varices. J. H. GARLOCK AND M. L. SOM. *J.A.M.A.*, 135: 628, November, 1947.

The authors suggest a new treatment for esophageal varices by a simple surgical procedure: packing of the posterior mediastinum through a cervical incision. Two patients with repeated severe hemorrhages from esophageal varices have had no further bleeding since cervical mediastinotomy 7 years ago and 2 years ago respectively. Follow-up esophagoscopies have shown disappearance of the varices. The mechanism by which the mediastinal packing acts to cause disappearance of the varices is not known, but it is suggested that new peri-esophageal venous collaterals may be produced in the upper posterior mediastinum which relieve the strain on the lower esophageal venous system.

Postappendectomy Incisional Interstitial Inguinal Hernia. E. E. JEMERIN. *Surgery*, 22: 852, November, 1947.

A case of a hitherto undescribed variety of hernia is reported. The hernia, a postappendectomy, incisional, interstitial, inguinal hernia, descended from the lower angle of a right lower rectus incision posterior to the rectus and internal oblique (and transverse abdominis) muscles to enter the inguinal canal, which it then traversed. On clinical examination what appeared to be a typical reducible indirect inguinal hernia was found, extending through the external inguinal ring into the upper scrotum. The right rectus scar appeared to be solid and the hernia independent of it. Only at operation was the true relationship discovered. The pathogenesis of such a hernia is discussed and the importance of recognizing its true nature is stressed.

Observations on Spinal Fluid in Lymphogranuloma Venereum. W. LEIFER. *Arch. Dermat. & Syph.*, 56: 699, November, 1947.

The spinal fluid of 25 patients with acute lymphogranuloma venereum showed no cytologic or chemical alterations that could be considered significant of asymptomatic virus invasion of the central nervous system. Such asymptomatic virus invasion has been demonstrated by others without disturbances of the spinal fluid. In none of the 25 cases studied was there a biologic false positive Wassermann of the spinal fluid, and none has been recorded in the reported cases of lymphogranuloma venereum meningoencephalitis. Attention is called to the fact that the clinical picture and spinal fluid abnormalities of acute syphilitic meningitis and lymphogranuloma venereum meningoencephalitis are strikingly similar, except for the presence of a positive Wassermann of the fluid in the syphilitic cases.

Propionate Caprylate Mixtures in the Treatment of Dermatomycoses; with a Review of Fatty Acid Therapy in General. S. M. PECK AND W. R. RUSS. *Arch. Dermat. & Syph.*, 56: 601, November, 1947.

The use of the fatty acids in the treatment of mycotic infections was introduced by the

Dermatologic Department of the Mt. Sinai Hospital. The basis for this treatment was founded on the fact that sweat was found to be fungistatic because of its content of fatty acids. A review of the experimental background and the clinical experiences with fatty acid therapy in the treatment of dermatomycoses is given. The results of in vitro experiments and clinical trial of a mixture of propionates and caprylates in various types of fungous infections are enumerated. The propionate-caprylate combination seems to be more effective than any of the other fatty acids tried for these diseases.

Gingival Biopsy for the Diagnosis of Generalized Amyloidosis. I. J. SELIKOFF AND E. H. ROBITZEK. *Am. J. Path.*, 23: 1099, November, 1947.

Diagnosis of generalized amyloidosis may be difficult to establish clinically. Even the Congo red test has limited usefulness, being unable to demonstrate minimal or moderate amounts of amyloid. Biopsy of liver or spleen has occasionally been done, but has obvious disadvantages. Gingival biopsy is described: its rationale lies in the fact that in amyloidosis, many tissues are involved, including the gingiva. The latter is also very suitable for biopsy: it is accessible, resistant to infection, bleeds little and has few pain nerve endings. Biopsy technique is simple and uncomplicated. Gingival biopsy was done in 23 cases clinically suspicious of amyloidosis. Amyloid material was found in 19. Of interest was the finding that biopsy was positive in a number of cases in which the diagnosis could not be otherwise established, including cases in which the Congo red test was "negative." Thus, gingival biopsy is a simple, effective technique for the diagnosis of amyloidosis. However, a negative biopsy does not rule out amyloidosis.

The Differentiation of Mediastinal Tumor and Aneurysm by Angiocardiography. M. L. SUSSMAN. *Am. J. Roentgenol.*, 58: 584, November, 1947.

Angiocardiographic visualization of the heart and great vessels is an important aid in the elucidation of mediastinal masses. Aneurysms ordinarily fill with diodrast along with their vessels of origin. At the same time, other abnormalities in the thoracic vascular structures may be demonstrated. The demonstration fails only when the aneurysm is clotted or when there is a small neck. By contrast, tumors do not impair the integrity of the large vessels except by compression and displacement. An exception is provided by malignant infiltration which may irregularly constrict or even occlude a large vessel.

Basal Metabolism of Children with Tumors. A. TOPPER. *Am. J. Dis. Child.*, 74: 669, December, 1947.

Data are presented showing that the basal metabolism of children with tumors of the brain is lowered, irrespective of the character of the tumor. The explanation for this may be found in reduced hormone stimulation, or reduced central nervous stimuli with decreased protoplasmic activity. In striking contrast to this, tumors elsewhere in the body, when malignant, cause a great increase in the basal metabolism. From the comprehensive studies of Warburg on cellular metabolism, it would seem logical to seek the explanation for the increased basal metabolism in the vigorous metabolism of tumor tissue *per se*, rather than in any extraneous stimulus. This suggests that the basal metabolism test may be a diagnostic aid in children in whom the presence of a tumor is suspected.

Urethane in Leukemia. J. J. WEBSTER. *J. A. M. A.*, 135: 901, December, 1947.

Webster reviews the pharmacology, world literature, and theories of mode of action, of urethane and other carbamates as used in leukemia and malignant neoplasia. Although thought to be relatively safe and non-toxic in normal human beings, the author thinks the present use of these drugs in neoplastic diseases warrants a word of caution. He reports a case representing the full selective effect of urethane on myelogenous leukemia. The patient suffering from a well defined myeloid leukemia, was treated by roentgen rays which caused a reduction of the white cell count, decrease in the size of the spleen and general improvement. Six months later, because of an exacerbation of the disease, urethane was

prescribed in 3 Gram daily doses. This was taken orally mixed with simple syrup or in capsules with magnesium oxide. After 11 days of medication, a selective inhibition of the early myeloid cells was noted. Weekly examinations indicated a decrease in the number of white cells, a rise in hemoglobin and red cells and diminution of splenic enlargement. Thirty-nine days (117 Grams) after beginning to take urethane, the patient complained of hemorrhagic phenomena, although at this time the white cell count was 24,000 and the hemoglobin was 80 per cent. Apparently the blood cell inhibition was so profound that 14 days after the withdrawal of the drug, and institution of transfusions, "pentanucleotide," and penicillin, the patient's white cell count was 100, cerebral hemorrhage occurred and death ensued. This is the fourth case reported of deleterious effects due to urethane medication: it is the second death. It is evident that there is some sensitizing factor in white cells, especially leukemia cells, which makes them susceptible to urethane and P^{32} , radioactive phosphorus. As to whether the mechanism of destruction depends on inhibition of oxidation, change in purine metabolism, substitution for cell deficiency, selective mitotic inhibition, or perhaps a maturation factor, is as yet unknown. The author concludes that urethane promises to be a valuable aid in the therapy of leukemia and perhaps in other diseases characterized by mitosis. Continued investigation is necessary to ascertain proper procedure, dosage, toxic levels and mode of action, before widespread use is advocated.

Technical Problems in the Surgical Treatment of Carcinoma of the Esophagus and Upper Stomach. J. GARLOCK. J. Thoracic Surg., 16: 215, 1947.

Radical resection of midthoracic esophageal carcinoma with high intrapleural esophagogastronomy is a great improvement over the old Torek procedure. For carcinoma of the lower third of the esophagus and cardiac end of the stomach, a combined abdominothoracic incision provides excellent exposure. The technical details of these procedures and the need for meticulous attention to pre and postoperative management and anesthesia are described in this article.

New Technique for Studying the Cytology of Gastric Aspirates in Man. F. HOLLANDER, M. HESS AND H. A. SOPER. J. Nat. Cancer Inst., 7: 365, 1947.

A method has been devised for increasing the cellular content of human gastric aspirates, using 5 per cent eugenol as a stimulus, after fasting secretions (control specimens) have been aspirated. The emulsion is administered via Rehfuess tube and allowed to remain in the stomach for 15 minutes. Gastric mucous secretion so induced is aspirated at 15 minute intervals following withdrawal of stimulus. The specimens thus obtained are smeared and stained with toluidine blue, for study of desquamated epithelial cells, singly and in groups. It is hoped that this method will lead to a technique for early cytological recognition of pathologic conditions of the stomach, including adenocarcinoma.

Comparison of Eugenol with Other Stimuli for Gastric Mucus Secretion. F. HOLLANDER AND F. U. LAUBER. Abstracts of Communications, XVII International Physiological Congress, Oxford, p. 155, 1947.

The characteristics of gastric mucous secretion obtained after applying eugenol emulsions to the mucosa of dogs' Heidenhain pouches were studied. These characteristics include viscosity, opacity, color, pH, columnar cell content, etc. Analysis of the results in relation to secretions induced by other mucus stimuli, led to the following conclusion:—Eugenol is an effective stimulus for gastric mucus secretion and has the advantage over clove oil of being a pure chemical individual. Clove oil, of which eugenol is the major component, had previously been found to be superior to other mucus-secreting substances investigated.

Group Psychotherapy in America. WILFRED C. HULSE. Swiss Arch. Neurol. & Psychiat., 110: 199, 1947.

The different approaches to group psychotherapy are described and evaluated under five headings: Group Therapy in the Armed Services; Therapeutic Play, Activity, and

Interview Groups; Psychodrama; Group Psychotherapy with Psychotic Patients; Group Therapy Through Self-organization of Patients (Clubs). The relations between individual and group psychotherapy are discussed. Limited use of didactic and inspirational methods for orientation of large groups seems effective. Better results are obtained through small, analytically oriented groups of well selected patients, especially children and adolescents. The value of group psychotherapy as a means to promote better understanding of the psychotic patient in large mental institutions is emphasized. More research concerning selection of patients and intra-group relations is urged. Better facilities for training in group psychotherapy are needed.

The Size of the Pulmonary Valve. E. S. HURWITT. Bull. Internat. A. M. Museums, 27: 170, 1947.

The protocols of 1000 consecutive autopsies on infants and children, excluding those with cardiac lesions, were reviewed with reference to the size of the pulmonary valve. The cases were divided arbitrarily into age groups and subjected to statistical analysis. The average dimensions of the normal pulmonary valve in the younger age groups were tabulated.

Subphrenic Abscess Following Primary Closure for Pilonidal Sinus. E. S. HURWITT. New England J. Med., 237: 398, 1948.

A case is reported in which primary closure of the defect caused by excision of a pilonidal sinus was followed by a hectic course in which a fatal issue was narrowly averted. It is suggested that the primary closure of pilonidal wounds be reserved for cases conforming to limited criteria. In the hands of the less experienced surgeon, or in the presence of recent inflammation, the procedure of total excision, packing the wound widely open and permitting healing by granulation may be indicated.

Surgical Procedures in Periodontia. M. L. MORRIS. New York J. Dentistry, 17: 303, 1947.

The various standard operations employed in advanced cases of alveolar bone loss are discussed and compared. These methods eradicate periodontal pockets by removal of overlying gingival and bony tissue when more conservative techniques are inadequate.

Pharmacology and Toxicology of Streptomycin. E. P. PICK. Hebrew M. J., 2: 184, 1947.

Cultures of streptomycetes griseus produce, according to studies of S. A. Waksman, streptomycin, one of the most valuable antibiotics. This differs from penicillin which acts on gram-positive bacteria, in that streptomycin is effective particularly in infections caused by gram-negative bacteria, i.e., against *Escherichia coli*, *Eberthella typhi*, *Pasteurella tularensis*, *Hemophilus influenzae*, *Mycobacterium tuberculosis* and others. This antibiotic seems to act especially against *aerobically* growing bacteria while anaerobes are not susceptible; its action may be due to its ability to block oxidative enzyme-systems essential for the growth of aerobic bacteria. The *chemical investigations* on crystallized streptomycin indicate that this complex molecule ($C_{21}H_{39}N_7O_{12}$) is built up of two basic fractions: one is *Streptidine* (2,4,5,6-tetrahydroxy-1,3-diguanido-cyclohexane) which is attached through a glycoside linkage to another complex the nitrogen-containing, disaccharide-like *Streptobiosamine*. Streptomycin is relatively stable in contrast to penicillin; solutions remain unchanged for three weeks at 37° C.; a heating for 10 minutes at 100° C. produces an inactivation of less than 50 per cent. Reducing agents, however, i.e. ascorbic acid, Ketones, cysteine, thioglycollic acid antagonize the antibacterial power of streptomycin. The antibacterial power of streptomycin is defined according to Waksman in L-units, an amount that inhibits growth of *colibacteria* in 1 liter of nutrient medium and a G-unit of the pure streptomycin base equalling 1000 L units or on a weight basis 1 mikrogram of streptomycin base is equivalent to 1 unit. The therapeutically effective concentrations vary with the type of organism as well as the individual strain.

The pharmacological and toxicological reactions of purified preparations show that the earlier toxicological reactions as nausea, headache, flushing of the skin and occasional fainting were due to an histamine-like impurity. The purified samples have no circulatory effects in therapeutic doses; only large doses produce in animals hepatic and renal changes. Important are, however, labyrinthine and vestibular disturbances after intramuscular administration of large doses, especially after intracisternal injection of 1000-1250 units per Kg. in dogs. Other side-reactions consist of skin rashes, fever, pain in the joints and discomfort at the site of injection.

Streptomycin is readily soluble in water and saline and is rapidly absorbed after subcutaneous, intramuscular and intravenous injection. The intramuscular route is the one of choice, intrathecal or intracisternal injection of streptomycin produces high concentration in the spinal fluid. The oral or rectal administration has produced unsatisfactory results because of poor absorption from the gastrointestinal tract; oral administration may be used for preparation of patients in abdominal surgery and for the treatment of typhoid patients and carriers.

Beside the neurotoxic symptoms one of the most serious obstacles in the prolonged use of this antibiotic is the *development of streptomycin resistant strains*. It may be that some procedures, f. i. combination of streptomycin and penicillin and others will retard or inhibit the development of this drug-fastness.

Roentgenologic Diagnosis of Diseases of the Urinary Tract. M. L. SUSSMAN. Diagnostic Roentgenology, 2: 583, 1947.

This is a long and comprehensive chapter in the volume.

A Discussion of Angiocardiograph and Angiography. M. L. SUSSMAN AND A. GRISHMAN. Advance in Internal Medicine, 2: 102, 1947.

This is a long and comprehensive chapter in the volume.

Book Reviews

Atlas of Oral and Facial Lesions. BY RALPH HOWARD BRODSKY, D.M.D., Associate Dental and Oral Surgeon, Mount Sinai Hospital, Consulting Oral Surgeon of the Department of Hospitals of New York City. 130 pages, 100 color slides, Baltimore, Maryland. The Williams & Wilkins Company, 1948. Price \$80.00

The potentialities of color slides to depict, with dramatic realism, the minutest details of surface lesions, have been taken advantage of for the first time in this new Atlas of Oral and Facial Lesions. Those engaged in clinical photography have long recognized that the brilliant illumination and magnification of the projected transparency is revealing of clinical features often not observable under normal lighting. For group study, such material is therefore of the greatest value.

This atlas makes available one hundred cases selected from the author's large collection of clinical photographs. Accompanying the slides is a textbook which describes the important features of each illustrated disease entity. There are forty representations of benign local conditions such as ranula, fibroma and torus palatinus, and thirteen illustrations of oral and facial malignancies. The remaining forty seven cases comprise a review of the oral manifestations of systemic diseases, including such examples as Addison's, lupus erythematosus, erythema multiforme, syphilis.

In general the slides are of excellent quality and the only criticism that might be ventured is in regard to the choice of material. This reviewer is acquainted with Dr. Brodsky's excellent collection, and unquestionably many of the fourteen cases of tuberculosis (an unwarranted apportionment for this disease) might have been omitted in favor of other more commonly encountered conditions.

The one hundred thirty page text is well written and concise. Though brief, it is adequate and serves the author's intention to supplement and clarify the visual portion of the Atlas.

Undoubtedly this fine work, the first of its kind, will be the forerunner of similar undertakings in other specialty fields of Medicine and Surgery. As such, Dr. Brodsky's work represents a major contribution quite apart from the intrinsic worth of the Atlas itself.

LEON EISENBUD, D.D.S.

Treatment in Proctology. BY ROBERT TURELL, M.D. Baltimore, Md. The Williams & Wilkins Company, 1949. 248 pp. Price \$7.00

As the title of this book suggests, it aims to place in the hands of the clinician in general and the proctologist in particular a useful guide for the treatment of diseases affecting the anus, rectum and colon.

Accordingly the emphasis throughout this concise and clearly written volume is on therapy, while diagnostic steps, pathogenesis and pathophysiology are referred to only wherever these are essential for a clearer understanding of the why and wherefore for recommended forms of therapy.

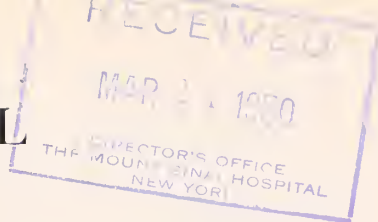
Not without merit are the descriptions of ingeniously designed instruments, which without doubt are a significant addition to the armamentarium of the proctologist.

A discussion of the use and advantages of the several chemotherapeutic and antibiotic agents is brought up-to-date. Ano-recto-colonic disorders as encountered in the young, the aged, and in the emotionally unstable receive understanding consideration.

The book is rich in illustrations, many of which are in color, adding much to their value.

E. H.

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BRAIN TUMOR, ITS MORPHOLOGY IN RELATION TO PROGNOSIS¹

JOSEPH H. GLOBUS, M.D.

Before opening a discussion of this highly important topic, it is necessary to define and delimit its scope. This applies particularly to the term "tumor". The latter, when correctly used, is applied to any form of expanding lesion in any location. Intracranial tumor denoting, as it does, any type of space-occupying lesion within the cranial cavity is employed to include such lesions as aneurysms, parasitic cysts, brain abscesses, gummas or other types of granulomas, and, above all, neoplasm. It is the last form of tumor which I shall consider at this time.

Even with the foregoing delimitation of the subject, it is necessary to introduce certain definitions and this, in turn, will serve to introduce the more significant subtopics for consideration, such as: Brain tumors in relation to intracranial tumors; Primary, true brain tumors; Primary, false brain tumors; and finally, Teratoid (autochthonous) tumors.

The term *brain tumor* is often used interchangeably with that of *intracranial tumor*. There is, however, an obvious distinction: the former is a tumor of the brain, its meningeal coverings or of some intimately related structure, such as the pineal body or pituitary gland. Intracranial tumor is a more general term, embracing not only the aforementioned but also other space occupying lesions in the cranial cavity, such as exemplified by osteoma of the skull and Schminke's lymphoepithelioma.

The term *primary brain tumor* needs little explanation—it denotes a neoplasm which takes its origin from the brain tissue proper; some of its cellular components; its coverings, the meninges; or its vascular apparatus. When primary tumors are derived from, and predominantly composed of, neuroectodermal elements, they are considered to be *true* primary brain tumors, while those which are derived from the meninges, for instance, are *false* primary brain tumors. The term secondary brain tumor is obviously used to designate neoplastic lesions metastatic in nature.

In another category, irrespective of the germinal layer of origin, are the autochthonous neoplasms, which include pinealoma, craniopharyngioma, infundibuloma and pituitary adenoma.

Two other terms to be considered are the often used appellations, *malignant* and *benign*—terms which need additional clarification when employed in connection with intracranial tumors. In general it may be said that a brain tumor may be regarded as malignant when it defies any competent therapeutic measure

¹ From the Department of Neuropathology, The Mount Sinai Hospital, New York.

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and leads to a fatal termination. Its malignancy is determined not only by its cellular structure, but also by its location, if it occupies a vital area of the brain and thereby makes its removal incompatible with continued useful life. A tumor is also ultimately malignant if, in spite of its benign cellular characteristics, it is inaccessible for surgical intervention.

The term *benign tumor* should, therefore, be restricted to a relatively small quota of intracranial neoplasms. These must be structurally benign, their location must be such as to be accessible for thorough eradication, and to permit removal without compromising the essential functions of the brain.

The foregoing statements defining brain tumor and the intrinsic qualities of its several types are based upon the study of a large number of brain tumors observed at The Mount Sinai Hospital in the course of more than 25 years. They include a great variety of tumors, differing from one another by their histologic character, location and size.

As already indicated, the present discussion is concerned primarily with the presentation of criteria which would enable one to predict the behavior of a given tumor and to select those in which a forecast of a favorable surgical outcome can be made. It should be obvious that such criteria regarding the behavior of a brain tumor and its effects upon its host depend to a great extent, if not altogether, on the morphologic features of such a lesion and its effect on the brain harboring it. Thus, it will be necessary to review briefly the present understanding of the nature, and the accepted classification of brain tumors.

CLASSIFICATION OF BRAIN TUMORS

It is generally assumed that brain tumors of the neoplastic variety are best understood in the light of the histogenetic and oncogenetic processes affecting the development of the brain, its appendages, and its coverings. To this may be added the vessels of the brain, which, in the final analysis, are derivatives of one of the three coverings of the brain.

Brain tumors, neuroectodermal in origin. At this point, as first consideration is given to one of the main categories of brain tumors, one which includes those of neuroectodermal origin, it will not be difficult to recall the several events in the embryogenesis of the central nervous system. There is at first the neural plate which is followed by the formation of the neural folds and the enclosed neural groove. With the fusion of the neural folds to form the medullary tube, a progressive thickening and cellular enrichment of the wall of the latter results in the formation of a layer known as the *matrix*, or the *mantle* layer. In the course of this early process, there can be recognized a separate aggregation of cells branching off from the medullary tube to form the neural crest. Within the mantle layer and the neural crest, there are at first a collection of primitive, undifferentiated cells, the so-called "parent cells" or "mother cells" (fig. 1) which, through a process of cell division and cell differentiation, maturation, give rise to the physiologically ripe elements of the central nervous system. The latter includes the nerve cells—often referred to as ganglion cells—and the glial elements, which constitute the supporting and nourishing cell forms of the brain. However, between the undifferentiated parent cells of the matrix of the medul-

lary tube and their final products, the mature cell forms in the fully developed brain, there are many transitional cell types (figs. 2, 3, & 4). Of these, only a few have been tagged with a name. I shall mention only those which have a significant bearing on the modern classification of tumors of neuroectodermal origin.

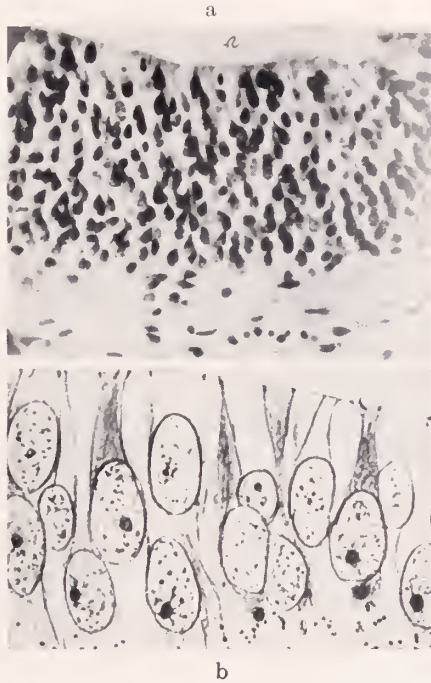


FIG. 1a. The appearance of undifferentiated neuroepithelium, (after Held)
 b. The appearance of neuroepithelium in very early phase of differentiation (after Held).

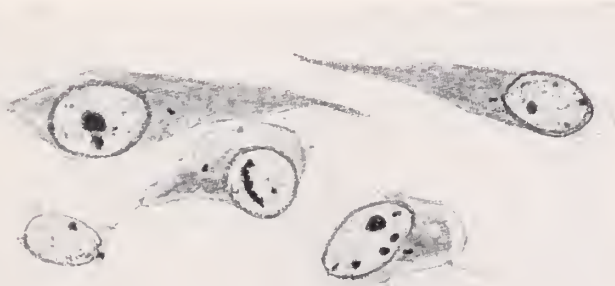


FIG. 2. Spongioblasts as seen in the normally developing nervous system, (after Held).

The latter is in accord with the histogenetic phases in the development of brain tissue elements as shown in the accompanying scheme (chart 1).

Neuroepithelioma: The aforementioned schematic outline (chart 1) illustrates the view that one type of neuroectodermal brain tumor springs from, and dupli-

cates, the appearance of primitive neuroepithelium, which consists primarily of parent cells (fig. 5). Such a tumor, which is often designated as *neuroepithelioma*, does occur, but not commonly, because in the course of its growth, many of the parent cells lose their primitive character and assume a more differentiated form.

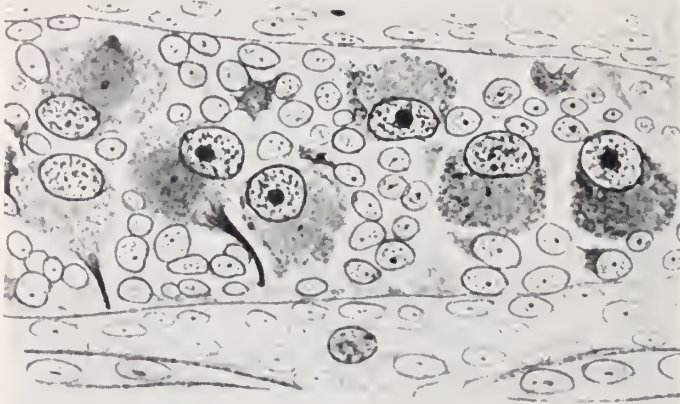


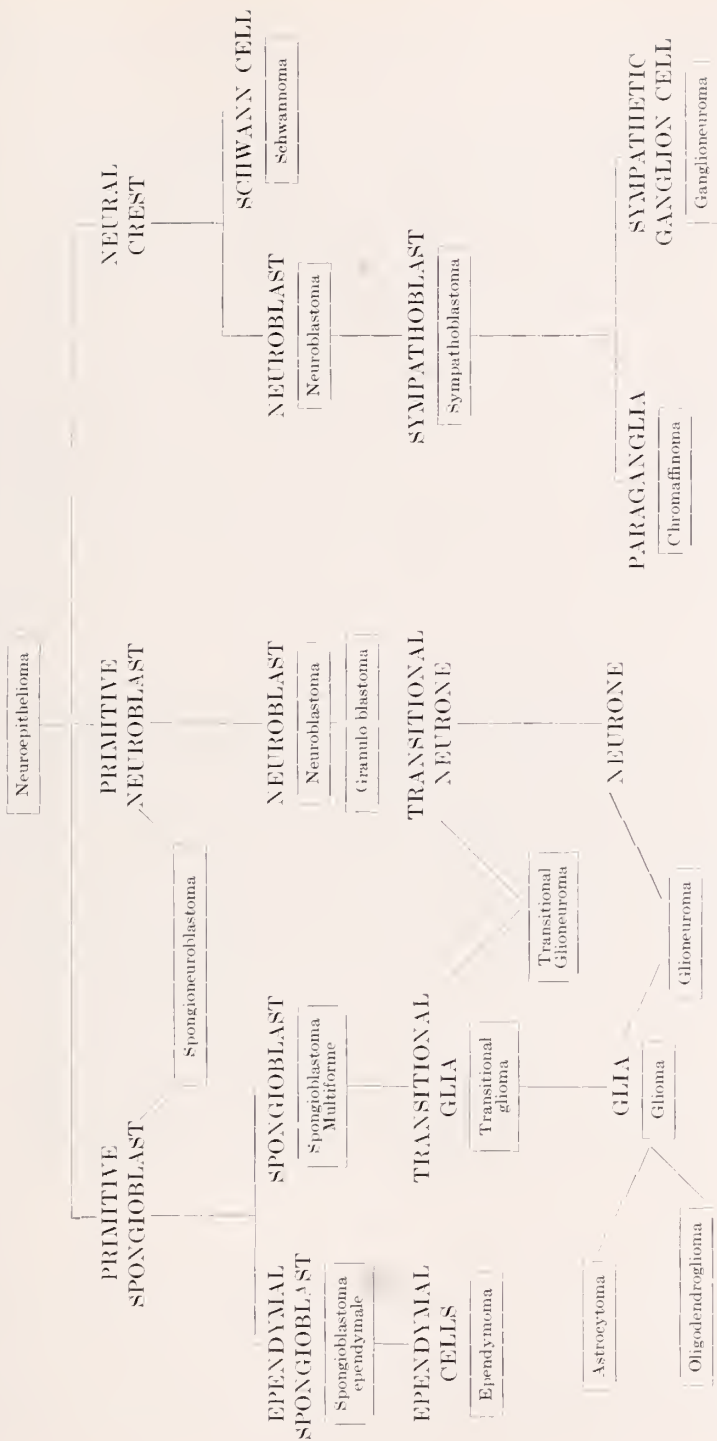
FIG. 3. Neuroblasts, displaying early axone formation, (after Held).



FIG. 4. Neuroblasts, in a more differentiated phase of development, (after Held).

A consideration of this type of tumor invites a restatement of an established criterion that *the lower the differentiation of a cell, that is the more primitive it is, the greater is its potency for growth*. Thus, it may be said that the more primitive a neuroectodermal tumor and this is true of neuroepitheliomas—when measured in terms of rapidity of growth, invasive character, and recurrence, the greater its malignancy.

CHART 1
NEUROEPITHELIUM
(Bi-potential parent cell)



A schematic outline of the histo-genetic stages in the development (maturation) of the neural, glial and ependymal elements of the nervous system with an indication of their relationship to the several forms of neoplasms, neuroectodermal in derivation.

The parent cell, in its process of division and differentiation, manifests a *bi-potentiality*, a capacity for producing cells which differentiate either into *spongioblasts*

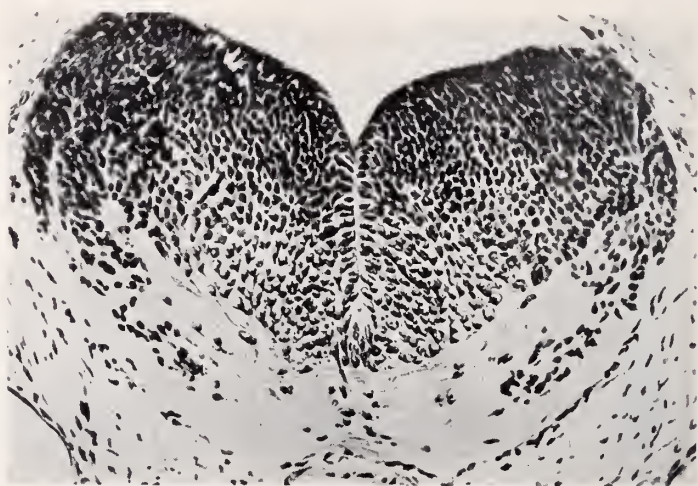


FIG. 5. Section of the medulla oblongata showing a wide zone of aggregated neuroepithelium in a low state of differentiation: some cells exhibit neuroblastic orientation (after Hiss).

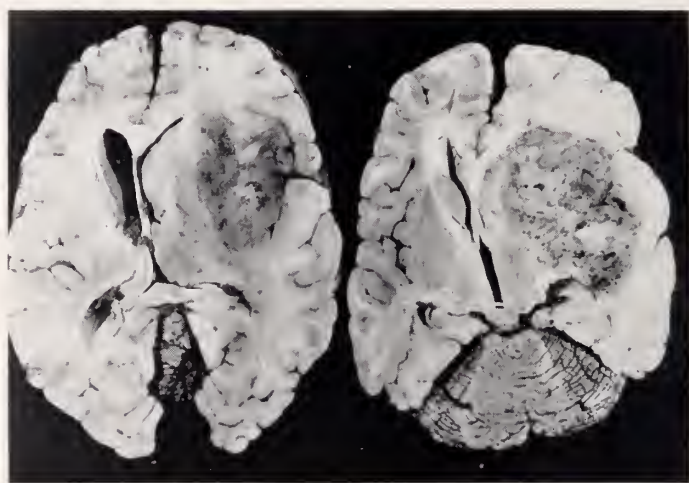


FIG. 6. Coronal section of a brain showing location and appearance of a spongioblastoma multiforme.

blasts or *neuroblasts* (figs. 3-5). These spongioblasts and neuroblasts represent more mature, but still transitional cell forms advancing toward maturity. Of these the spongioblasts, the forerunners of the gliae cells, have retained much of the growth potentialities of the parent cell.

Spongioblastoma multiforme: In accordance with the foregoing it can be readily realized that spongioblasts, the forerunners of the supporting glial elements,

must be ever ready to meet the constant structural needs of the brain. This explains why tumors composed of large numbers of spongioblasts are in the majority and why they are designated as spongioblastoma multiforme. The modifying term "multiforme" is added to indicate the great morphologic variability in this type of neoplasm. The low grade of differentiation of its dominant cell form is, of course, responsible for its rapid and extensive growth and hence for its malignancy.

At this point another departure is made, even at the risk of being redundant, in order to clarify further the term malignancy as it is applied to brain tumors. Generally speaking, a tumor is considered to be malignant if it is invasive, rap-

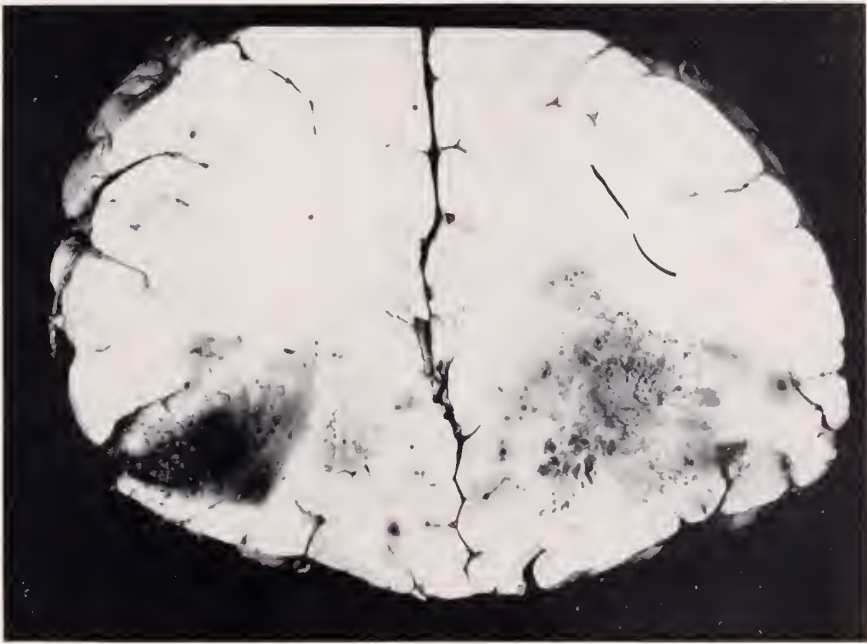


FIG. 7. Coronal section of a brain showing multiple growth centres of spongioblastoma multiforme.

idly growing, highly vascular, and capable of metastasizing. All these criteria for malignancy apply also to brain tumors, but in the latter there are other features which add to the malignant character of the tumor, for by malignancy it is necessary to regard any other related factor contributing to a fatal outcome in the affected case. The brain tolerant as it is to expanding and even to some destructive lesions, in view of the vital part it has assumed in the life functions of the individual and because of the centralization of the structural elements controlling these functions, often reaches a point where it is no longer capable of rendering useful service as the result of invasion, compression or distortion caused by an expanding lesion. Therefore, a rapidly growing, invading, thereby displacing, distorting tumor such as *spongioblastoma multiforme*, displays all of the threaten-

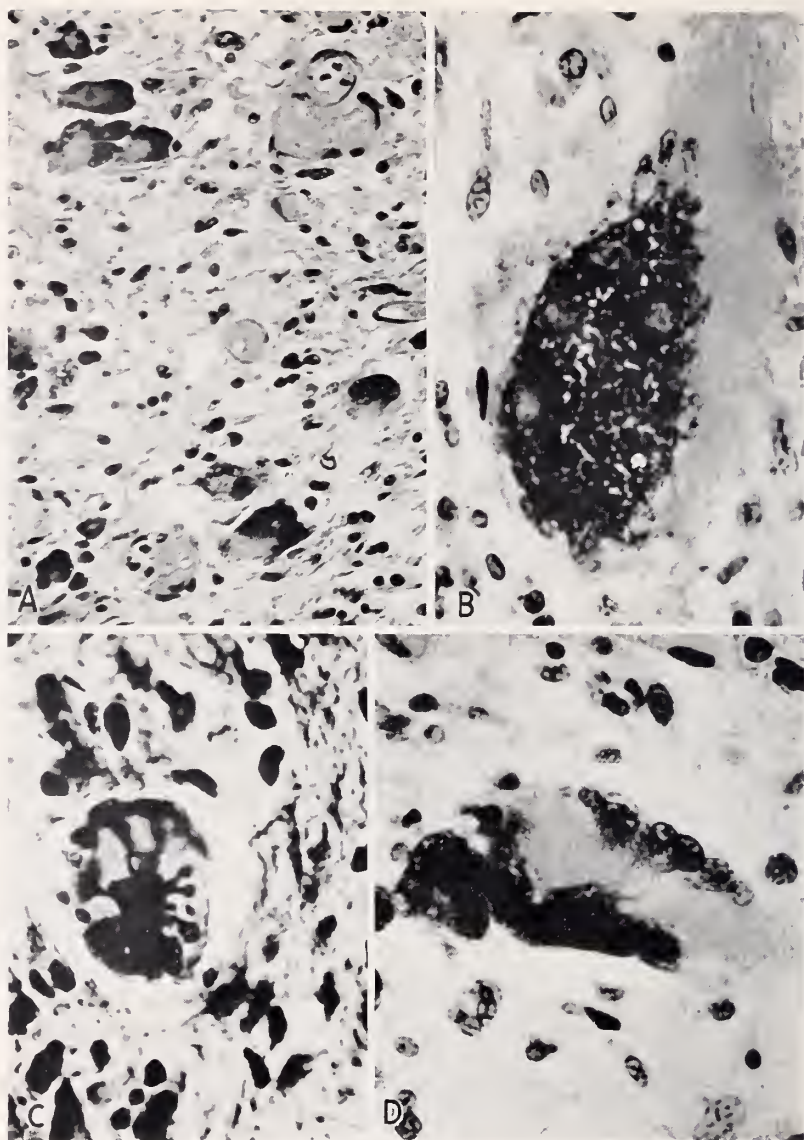


FIG. 8. Photomicrographs illustrating the several types of giant cells encountered in spongioblastoma multiforme. A-general appearance of giant cells and their irregular distribution. B- giant cells showing multipolar distribution of nuclei; C- giant cell with nuclear extensions; D- giant cell with nuclear threads.

ing features of a malignant tumor (fig. 6). Its malignant character is often further enhanced by its tendency to appear simultaneously in several parts of the brain as multiple centres of growth (fig. 7). Its histologic earmark, the giant cell, (fig. 8) offers a reasonable explanation for its rapidly progressive growth: the giant cell, so to say, exploding into a large number of cells, thus causing rapid expansion.

The foregoing offers the theoretical basis for considering spongioblastoma multiforme as a malignant, and surgically unpromising tumor form. Two questions may be asked at this point: 1) does clinical experience support this conclusion? 2) what clinical criteria have we for the recognition of this type of tumor, and how safe can one be in predicting the results of surgical intervention?

As far as the first question is concerned, the answer may be found in the following summary of the postoperative results in 59 verified cases of spongioblastoma multiforme.

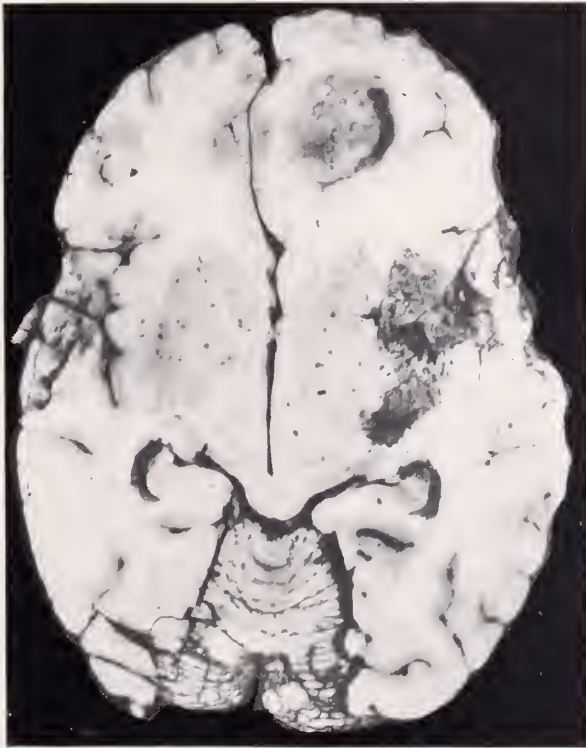


FIG. 9. Horizontal longitudinal section of brain showing location of a spongioblastoma in the frontal area, and another focus which contained a similar tumor and was partially removed by operation.

Survival Period

<i>1-6 days</i>	<i>1-3 weeks</i>	<i>1-4 months</i>	<i>6-9 months</i>	<i>1 year</i>	<i>3 years</i>	<i>4 years</i>
35	4	11	5	1 Br. ²	2 Br. ²	1 Rec. ²

The survival period in 16 unoperated cases of the same type was from 1 to 3 weeks.

To establish the malignancy of a given tumor, assuming, of course, the existence of an expanding intracranial lesion, it is necessary, above all, to establish its location and accessibility for surgical intervention. An inaccessible tumor of

² Br. = Bed-ridden; R = Regressing; Rec. = Recurrence

the brain, no matter how benign morphologically, must be considered as malignant. A sudden onset, rapid progression in the evolution of the signs and symptoms of increased intracranial tension, is strongly but not decidedly so, indicative of the malignant character of a tumor. In the presence of signs suggesting the

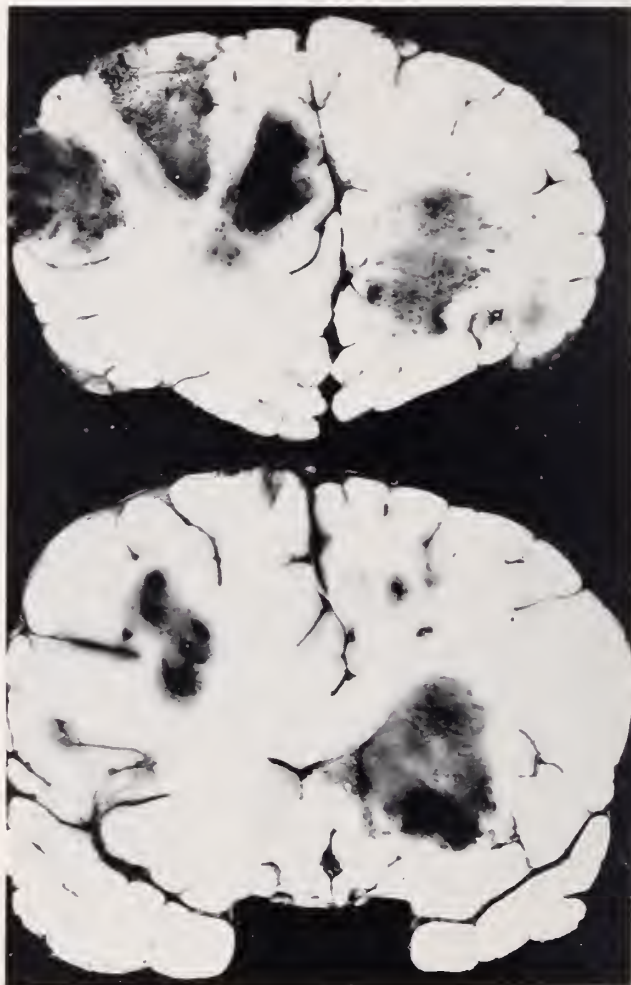


FIG. 10. Coronal sections of a brain, showing multiplicity of centres of growth in a spongioblastoma.

existence of a primary tumor elsewhere, such as revealed by chest plates or some constitutional disturbances, the metastatic nature of the tumor is, of course, most likely.

Spongioblastoma: Another tumor form, so named by me, is a type of neoplasm which is still under discussion. Some observers accept it, while others deny its existence. Chart 1 points to the probability that, if a parent cell is capable of giving rise to spongioblasts on one hand and neuroblasts on the other, then a

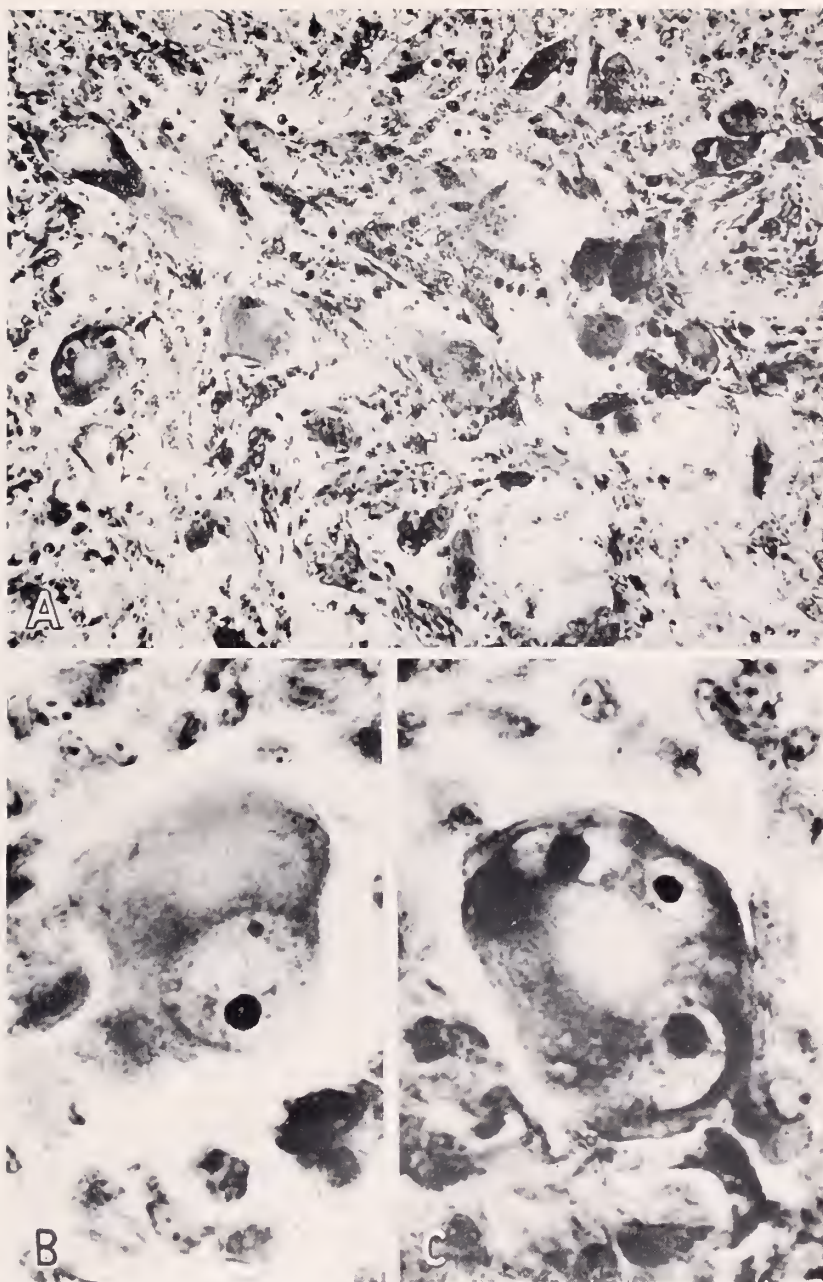


FIG. 11. Histologic appearance of a spongioblastoma, A- showing numerous neuroblastic giant cells; B- giant neuroblast with a single nucleus; C- giant neuroblast with several nuclei at the periphery.

number of such parent cells constituting a source of tumor formation may readily provoke the growth of a tumor in which both neuroblasts and spongioblasts will

participate in equal or somewhat varying numbers—hence the term *spongioneuroblastoma*. There is good reason for assuming that such a tumor is almost on a par with the spongioblastoma multiforme. Its rate of growth, multiplicity of centers of growth and effect upon the brain as a whole are features strikingly similar to those of spongioblastoma multiforme (figs. 9, 10, & 11). In fact, the spongioneuroblastoma and the spongioblastoma multiforme displaying some quite striking morphologic difference, cannot be distinguished from one another clinically. The promise of surgical success is no different in this type of brain tumor from that in spongioblastoma multiforme as shown in the following chart.

The postoperative results in 61 cases of this type of tumor were as follows:

<i>Survival Period</i>						
<i>1-6 days</i>	<i>1-3 weeks</i>	<i>1-4 months</i>	<i>6-9 months</i>	<i>1 year</i>	<i>3 years</i>	<i>7 years</i>
25	21	7	4	2 Rec. ³	1 Rec. ³	1 R. ³

The survival period in 12 unoperated cases was 1-2 weeks.

Transitional glioma: For some time after the term glioma was first introduced years ago, almost all fleshy tumors, primary in the brain, were designated as gliomas. Somewhat later, with the recognition of some features distinguishing several forms of glioma subgroups were established and were tagged as gliosarcomas when the tumor displayed an unusually rich cellular and vascular content or as alveolar and giant cell gliomas, in accordance with some histologic features. At the present time, the term glioma is still being used in some clinics, with the addition of modifying adjectives such as astrocytic (astrocytoma), astroblastic (astroblastoma), and fibroblastic. These names are used to indicate the benign character of such primary brain neoplasms in contradistinction to the frankly malignant spongioblastomas (often called glioblastomas).

In my own experience I find no justification for such designations as glioma implying a probable benign character. The objection is to be found in the mere fact that most probably there is no such tumor as a benign glioma. Every primary neuroectodermal tumor of the brain contains a centre (or nucleus) varying in size and consisting of undifferentiated hence potentially malignant cells. It is these centres (or nuclei) that provide the material for the progressive neoplastic growth. They also contain cells which determine the ultimate character of the tumor. The coexistence within the same tumor of relatively better differentiated cells, alongside the primitive or less mature cells does not mean that the tumor is histologically benign. In fact, even though it may have many mature glia cells, the basic character of a tumor containing them is determined essentially by the less conspicuous primitive or only partially differentiated cellular elements. Such a tumor may harbor among the parent cells spongioblasts and still more differentiated cell units, but it nevertheless cannot be called glioma and be thus considered as a benign tumor and hence as one no longer presenting the hazards of further growth. At best it can be considered as a form of transitional glioge-

³ Rec. = Recurrence; R. = Regressive

nous growth, for which I have suggested the term *transitional glioma*, because of the intermediary histogenetic character of its component glial elements. Not unfrequently errors are made in naming a tumor a benign glioma, because surgical specimens obtained by biopsy are often not representative of the tumor under investigation. They often contain mainly, if not exclusively, mature glial elements, components of a reactive gliosis about some other type of neoplasm, and

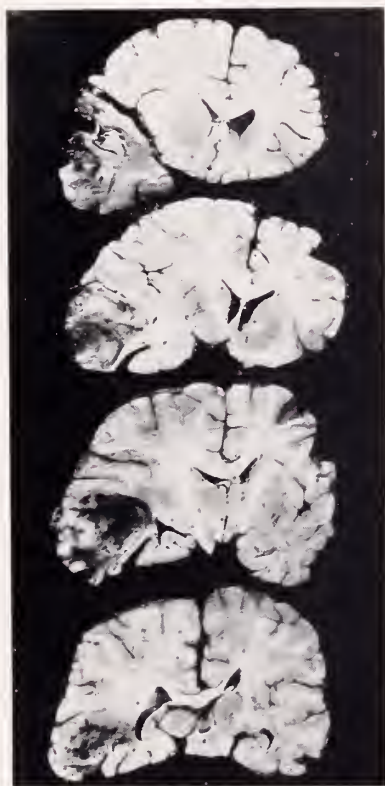


FIG. 12. Coronal sections of the brain displaying the hemispheric extent of a transitional glioma. The homolateral ventricles is compressed and the entire ventricular system is displaced to the opposite side.

are erroneously considered as the true elements of the growth, which is thus labelled glioma incorrectly.

Transitional glioma obviously, is not histologically benign—all that can be said is that it is a little less malignant than the spongioblastoma multiforme. Its extensive growth, often involving more than one lobe of a hemisphere and its frequent occurrence in multiple areas (fig. 12) also speak against its benign character.

Histologically there are some distinguishing features which are depicted in Figure 13.

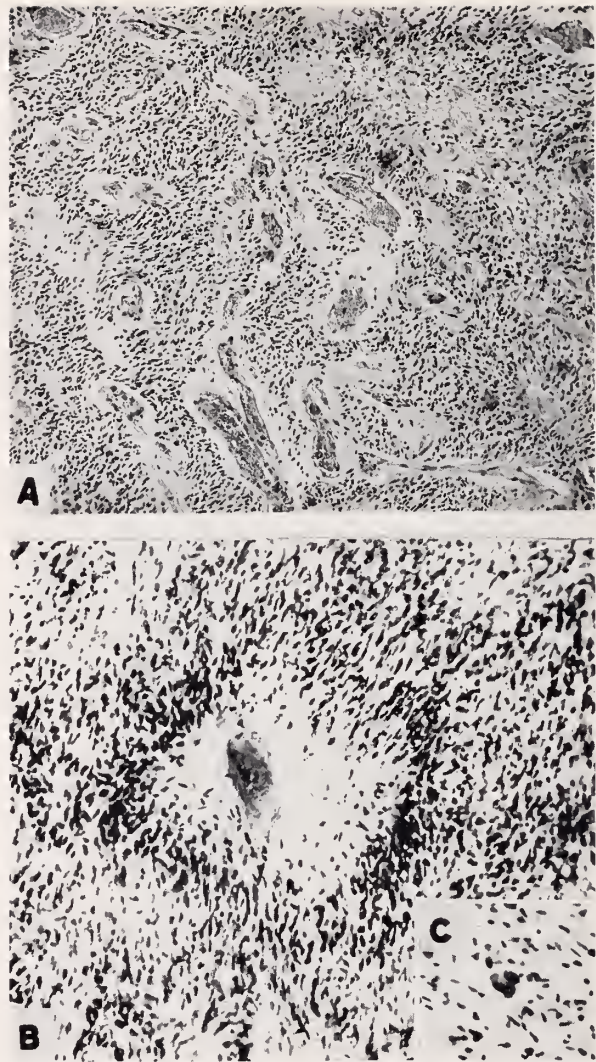


FIG. 13. Photomicrographs illustrating A- the structure of a transitional glioma; B-characteristic palisading of nuclei about a blood vessel; C-a multi-nucleated giant cells usually encountered in small numbers.

The post operative result of 40 cases of transitional gliomas

Survival Period						
1-6 days	1-3 weeks	1-4 months	6-9 months	1 year	2 years	3 years
20	1	1	4	5 Br.*	3 Br. ⁴ 1 Imp. ⁴	1 Rec. ⁴
		4 years	5 years	6 years	7 years	
		1 Rec. ⁴	1 Rec. ⁴	1 Rec. ⁴	1 Rec. ⁴	

Survival period in 10 non-operative cases—1 day to 3 weeks.

⁴ Br. = Bed-ridden; Imp. = Improved; Rec. = Recurrence; Unch. = Unchanged;

The same reasoning applies to what I choose to call *transitional glioneuroma*, a tumor which is dominated by cells of spongioblastic and neuroblastic lineages in a more advanced stage of development (figs. 14 & 15) but not fully mature.

The post operative results in 26 cases

<i>Survival Period</i>						
<i>1-6 days</i>	<i>1-3 weeks</i>	<i>1-4 months</i>	<i>1 year</i>	<i>2 years</i>	<i>3 years</i>	<i>7 years</i>
13	3	2	3 Br.	2 Br. 1 Unch.	1 Rec.	1 Rec.

Survival period in 3 non-operative cases 1 to 3 days.

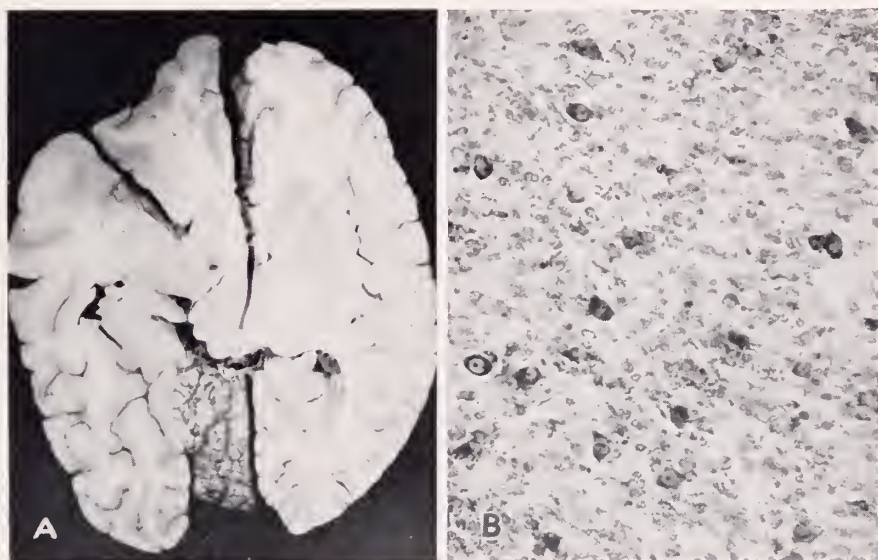


FIG. 14. A-Longitudinal horizontal section of a brain showing enlargement of a hemisphere, particularly its frontal area due to the presence of a poorly demarcated transitional glioneuroma. B- histologic appearance of the tumor, showing fairly ripe neuronal elements surrounded by the faintly staining glia cells.

Medulloblastoma: This name was introduced by Bailey and Cushing to designate a cerebellar tumor usually situated in the fourth ventricle (fig. 16). Originally they have used the name spongioblastoma to describe it, but subsequently, in order to distinguish it from the spongioblastoma already described by Globus and Strauss. Bailey and Cushing found an explanation for their term in the belief that these tumors consist of cells of both neuroblastic and spongioblastic lineage originating in a hypothetical medulloblast. It could, therefore, be grouped with the spongioneuroblastomas.

It is considered to be the most common form of brain tumor of childhood. It is histologically and clinically malignant, in view of its rapid growth, precarious location and tendency to spread by way of the subarachnoid space. Bailey recently said: "the only logical treatment for medulloblastoma cerebelli is complete removal, but this has so far proved impossible. However encapsulated the tumor may seem to be and however complete the removal may seem to have been, the

symptoms inexorably return in a few months. Even radiation, at first startlingly effective, causes but temporary improvement."

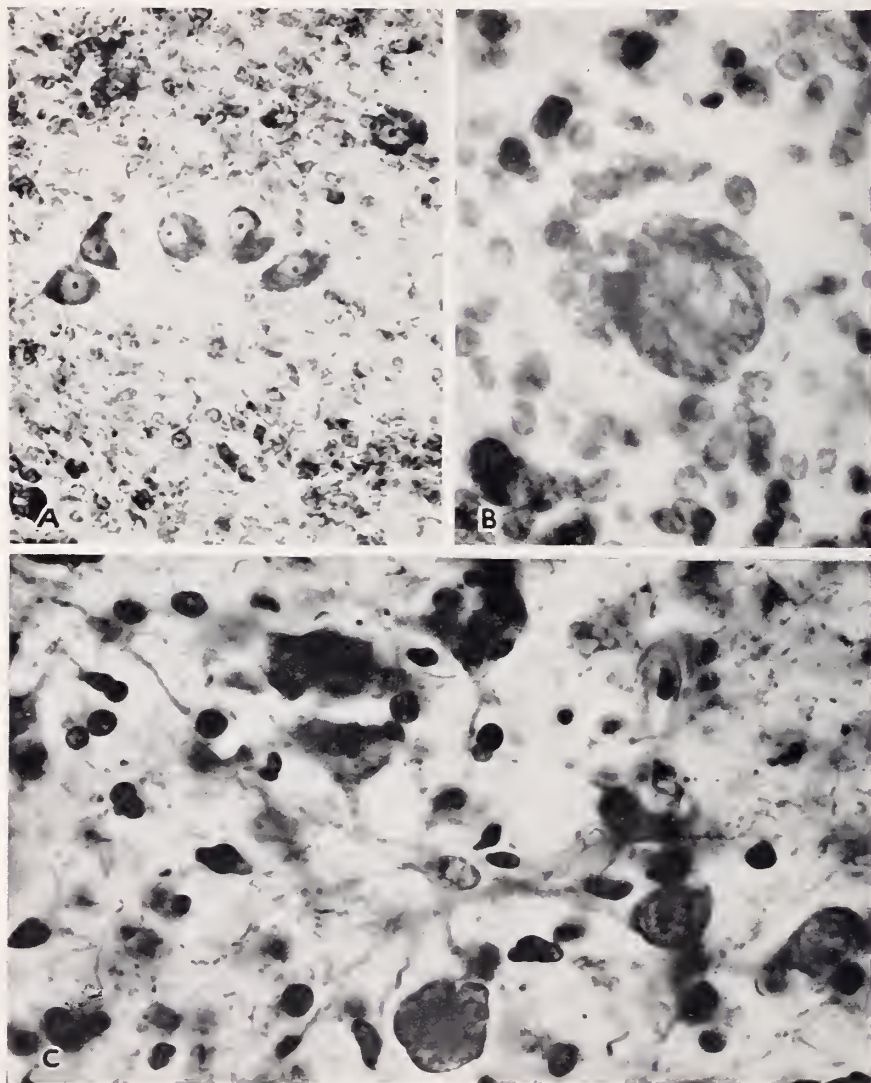


FIG. 15. Histologic features of a transitional glioneuroma. A- an area of fairly ripe nerve cells, surrounded by neuroblasts in various stages of transition; B- A giant multinucleated cell enveloped by capsule cells; C- well differentiated astrocytes and many other atypical glial elements.

Ependymoma: This is another form of gliogenous tumor which, as the name suggests, consists of cells which simulate the ependyma, the ventricular lining or subependymal plate, in some phase of their histogenetic transformation. Their

ultimate origin is, of course, from cells in the matrix which are destined to become ependyma, lining the ventricular surfaces or the surfaces of the choroid plexuses. Some of such tumors display so high a stage of differentiation as to duplicate closely the structure of the choroid plexus (fig. 17).

This type of tumor is in a large number of instances infiltrating and for this and other reasons surgically unpromising (fig. 18). There is a form of ependymoma which because of its low differentiation of its component cells I have designated as *spongioblastoma ependymale* (fig. 19). Here even more so than in the more differentiated, thus histologically less malignant ependymomas, be-

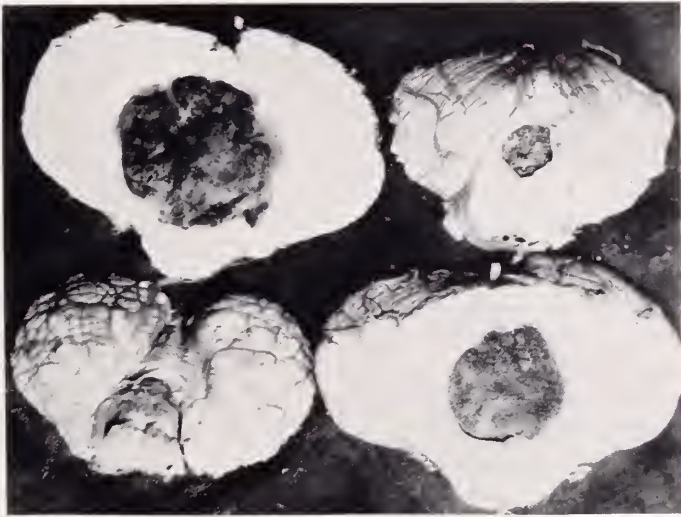


FIG. 16. Midsagittal section of a brain showing appearance and location of a medulloblastoma.

cause of the invasive character and proximity of the growth to ventricular cavities, the inaccessibility for surgical intervention is quite obvious (fig. 20). Indeed, there are a few recorded cases of well circumscribed ependymomas of the 4th ventricle in which surgical intervention was quite successful and was followed by a relatively long survival period.

Acoustic neuroma: A more common form of primary true brain tumor is the so-called Schwannoma, or acoustic neuroma. Its origin presumably stems from the component of the neural crest (see Chart 1). This, as an exception to the rule, is a neoplasm which by virtue of its cellular components has acquired a fair degree of maturation and is slow growing. No less significant is the usual location of this type of tumor in the ponto-facial angle, and hence its fair accessibility for surgical intervention. Because of the slow growth and the tolerance of the brain in such circumstances, early clinical recognition is an infrequent occurrence. But even when detected late in its development the only treatment available, and in this instance imperative, is surgical intervention. Success is deter-

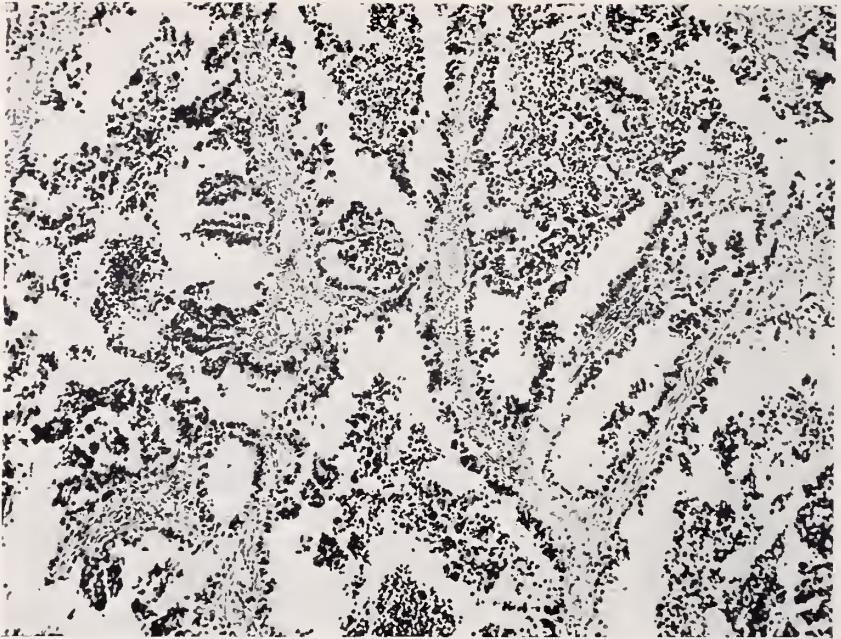


FIG. 17. Ependymoma, with the histologic appearance simulating that of the mature choroid plexus.

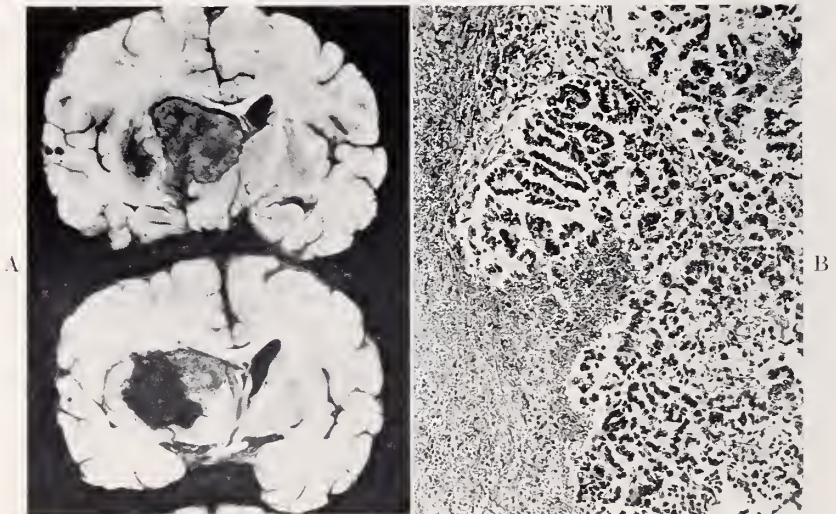


FIG. 18. A- Coronal sections of the brain showing the gross appearance of an ependymoma; B- Histologic appearance of the tumor for which the name papilloma choroideum is appropriate.

mined by the size of the neoplasm, its accessibility, and the state of the vascular bed (fig. 21).

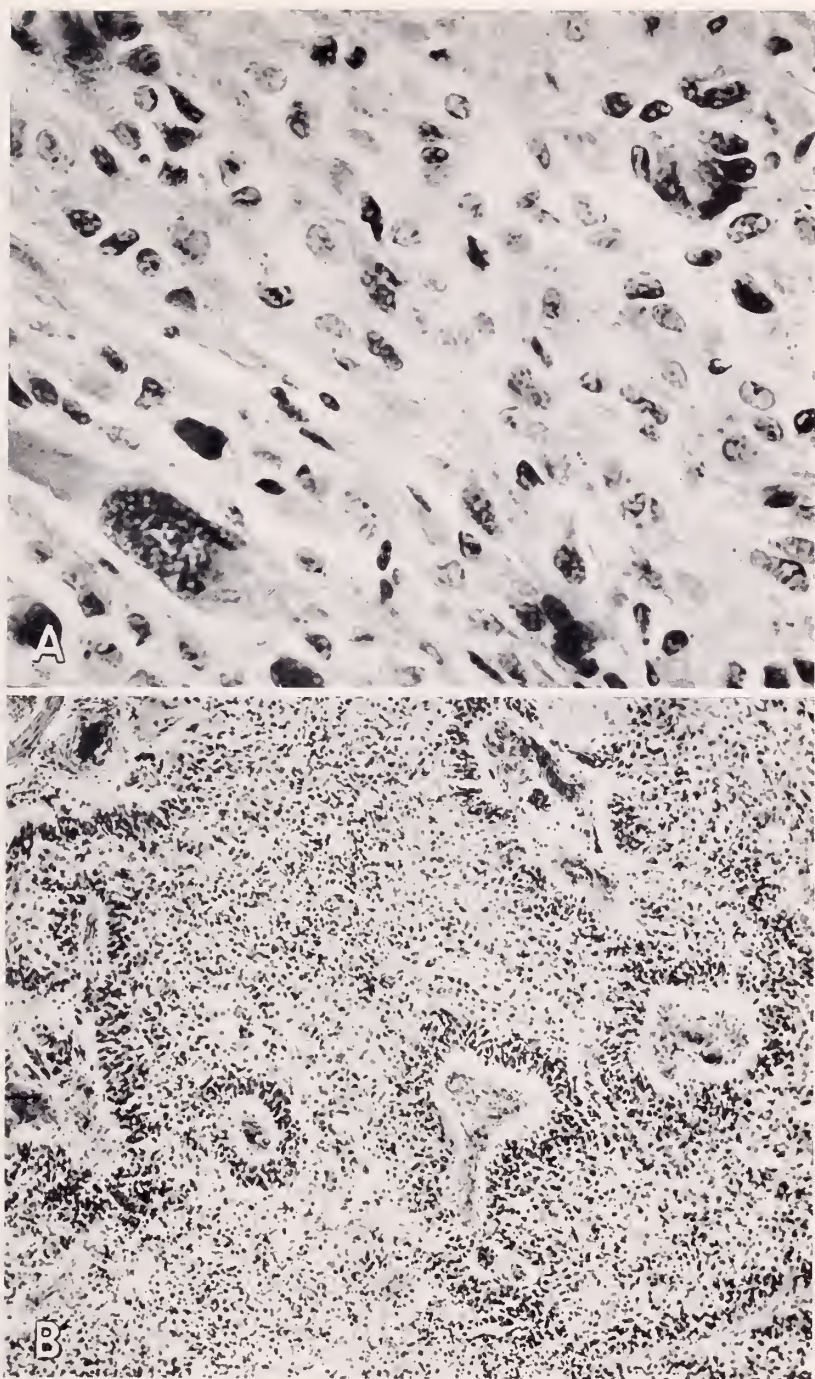


FIG. 19. Histologic appearance of a spongioblastoma ependymale, showing in: A- several giant cells, B- typical cell arrangements with cell columns aggregated about blood vessels.

Autochthonous brain tumors: Under this term are assembled brain neoplasms which are situated within a given structural unit or brain subdivision and which duplicate in a varying degree some phase in the histogenesis and cellular organization of the respective primordia from which they develop. Since such primordia may be displaced in an early developmental stage, the resultant tumor may be

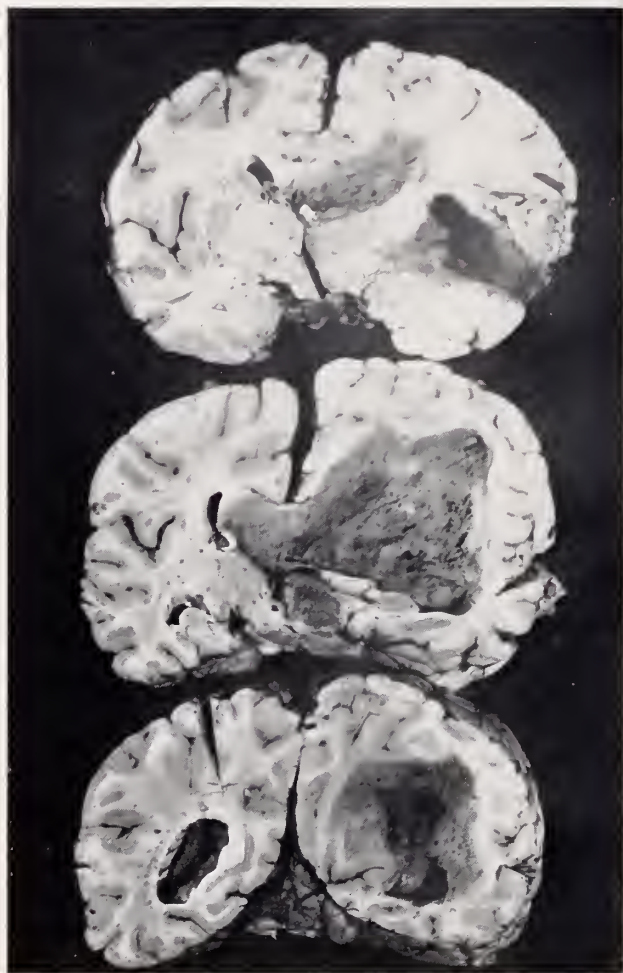


FIG. 20. A coronal section of a brain showing location and the infiltrating character of a spongioblastoma ependymale.

found in a location at some distance from the normal site of the ultimate structure it reproduced.

The craniopharyngioma is a fairly common type of tumor in this general category. It was named so by Cushing following the lead of Erdheim. Its source is the primordium of the anterior lobe of the pituitary gland, the so-called Rathke's pouch, or more precisely, a column of cells which may be traced from the oral cavity to this pouch, the so-called craniopharyngeal duct. Tumors derived from

these embryonal residues are usually cystic, (figs. 22 and 23) constituting the so-called suprasellar cysts. However, not uncommonly, they are solid (figs. 24 & 25) and exhibit the cellular features of adamantinoma. Generally the histological structure of these tumors is of a benign character, infrequently invading, but not uncommonly distorting or disrupting adjacent tissue or spaces.

More significant is their suprasellar location, bringing them in close proximity to the vital structures in the interpeduncular space at the base of the brain, which they often displace, compress and distort. Thus they are likely to disrupt



FIG. 21. The base of a brain showing location and site of an average acoustic neuroma.

the exceedingly important functions of the tuber cinereum, oculomotor nerves, mammillary bodies, parts of the optic chiasm and tracts, and nuclei in the lower portion of the third ventricle. They often cause obstruction of the flow of the cerebrospinal fluid from the lateral ventricle and cause internal hydrocephalus. It is thus readily seen how encroachment upon the several vital structures may cause dysfunctions which in the course of time become incompatible with sustained life.

What about surgical intervention in such instances? Certainly, little, if anything, can be accomplished in the case of the solid interpeduncular tumors be-

cause of their inaccessibility and the hazards of further compromising the structures in the interpeduncular space or the floor of the third ventricle. When the cystic variety of these tumors is considered it becomes obvious that radical removal is impossible for reasons not unlike those mentioned in connection with similarly located tumors of the solid variety. All that may be hoped for is the opening of the cyst and providing for its drainage. Aside from the frequent damage to the floor of the third ventricle, which is almost inescapable and incidental



FIG. 22. The base of a brain showing location and appearance of a craniopharyngioma.

to the nature of the operation, the results at best can only offer some temporary relief, but no lasting cure with full re-establishment of normal functions.

The pincaloma constitutes another not too uncommon type of autochthonous neoplasm. It originates from the primordium of the pineal body in the subependymal matrix and may duplicate in its histologic structure one or more phases in the histogenesis of that body. Most commonly it resembles the late fetal or early postnatal stage in development (figs. 26, 27), but occasionally more or less mature phases are represented. The pinealoma is usually histologically benign. Occasionally, when its cellular structure has retained a very immature form, it

assumes malignant characteristics not unlike those encountered in the spongioblastoma group. Here again greater consideration must be given to the location of the tumor. It is usually found in intimate relationship to the quadrigeminal plate (figs. 28, 29), the aqueduct of Sylvius and the underlying structures in the midbrain. One result of this crucial location is the closing of the aqueduct of Sylvius, resulting in internal hydrocephalus. This, in turn, causes distention of the third ventricle, and pressure atrophy of its floor with ultimate disruption of

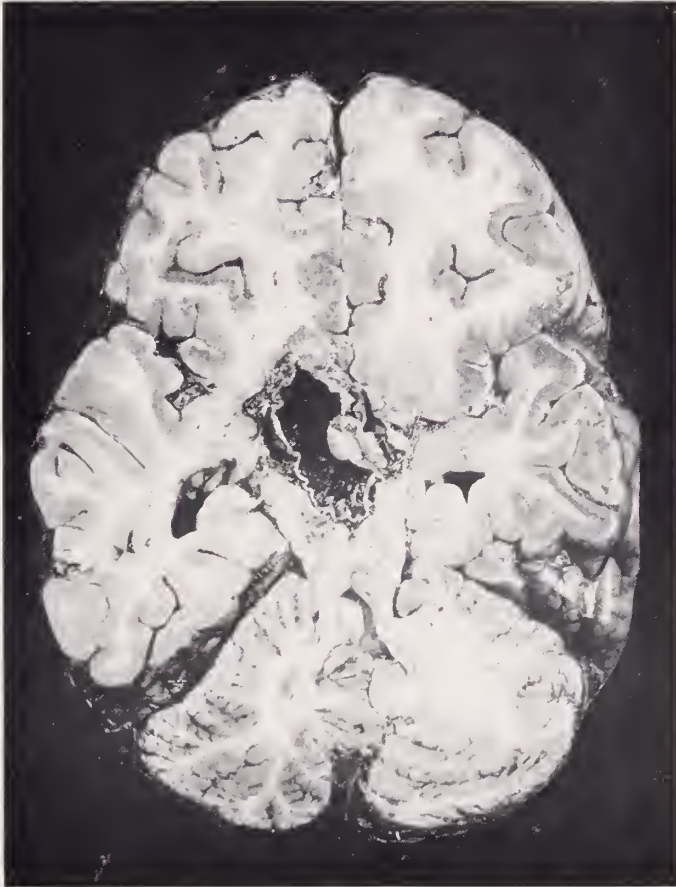


FIG. 23. Horizontal longitudinal section of the brain shown in figure 22, exhibiting the cystic character of the craniopharyngioma.

its important nuclei. Signs and symptoms of marked increase in intracranial pressure accompanied by vegetative disturbances are in the foreground. The involvement of the quadrigeminal plate and distortion of the oculomotor nuclei, cause disturbing eye muscle dysfunctions, and loss of hearing. Motor paralysis and sensory disturbances often are present as the result of the midbrain implication. Not infrequently this type of tumor extends into the rostral part of the brain (fig. 30).

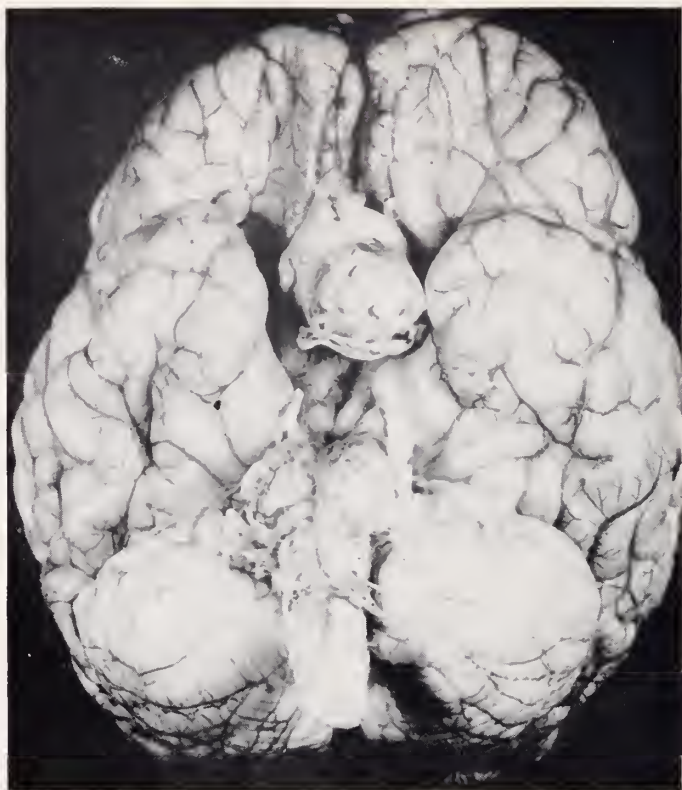


FIG. 24. The base of a brain showing the location and appearance of a solid form of a craniopharyngioma (adamantinoma).

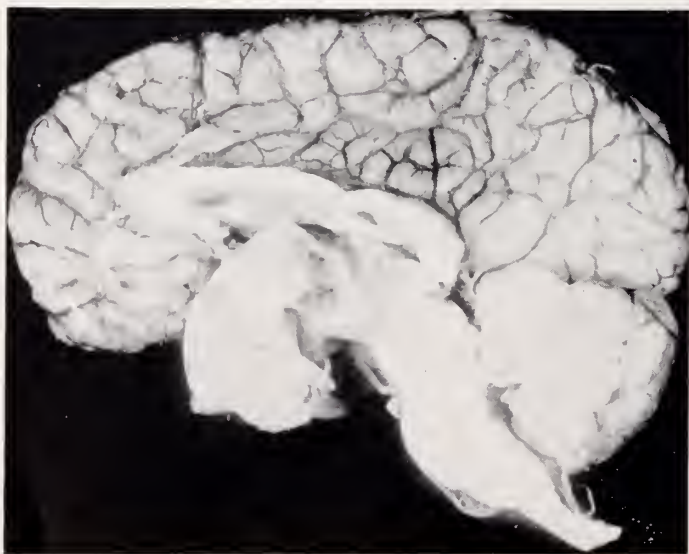


FIG. 25. Midsagittal section of the brain shown in figure 24, exhibiting the solid nature of the tumor.

Obviously, a lesion at this "crossroads of the brain", is a most disruptive force. Here, again, the question is what may be expected from surgical intervention? The answer is obvious and may be inferred from the fact that in recent years the neurosurgeons have completely abandoned any hope for surgical success in this

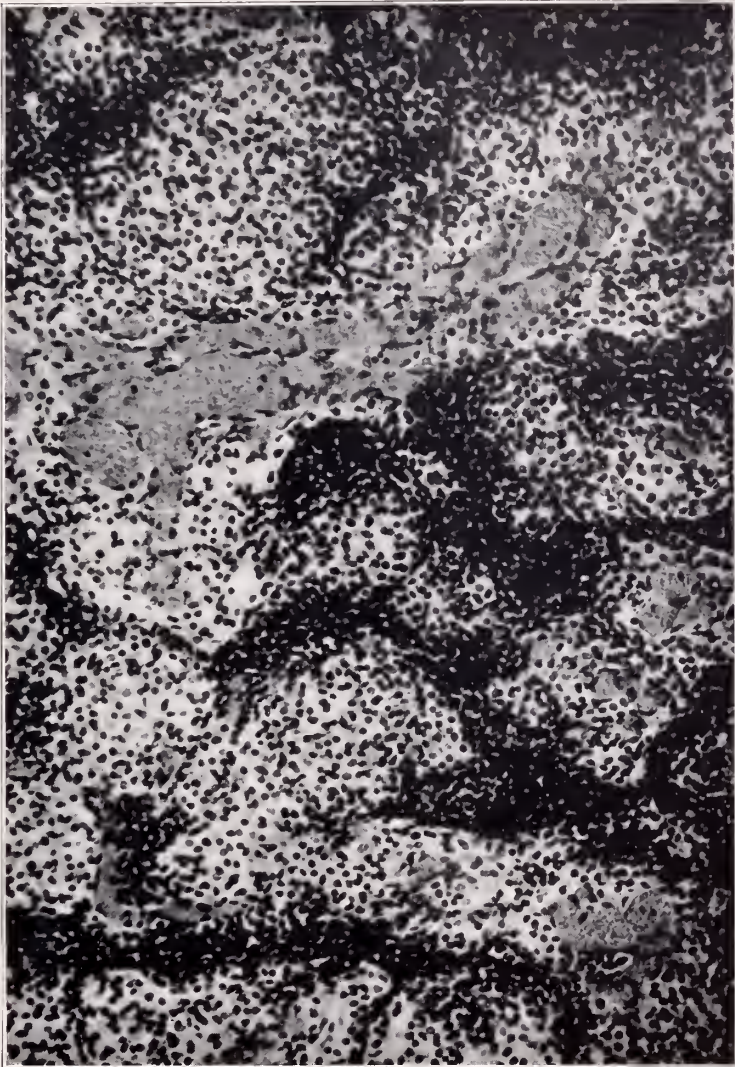


FIG. 26. Photomicrograph illustrating the histologic appearance of the normally developing pineal body in an infant of 28 days. Compare with figure 27.

type of tumor. The great operative hazards of complete removal and the futility of partial removal are, of course, the reasons for this attitude. The neurosurgeon has almost completely surrendered this type of tumor to the radiotherapist, for whose claim of success there is still no substantial proof.

This surrender, as already indicated, was not unconditional, as an operation was devised by the Danish neurosurgeon Dr. Torkildsen, which bears his name. It provides an artificial channel for draining the ventricular cerebrospinal fluid, thus reducing or removing (temporarily) the development and effects of any obstructive internal hydrocephalus. It necessitates the introduction of a rubber tube into one part of the ventricular system and connecting it with another channel more posteriorly, which drains the cerebrospinal fluid. The advisability of such a procedure raises serious problems, particularly one concerning its hazards.

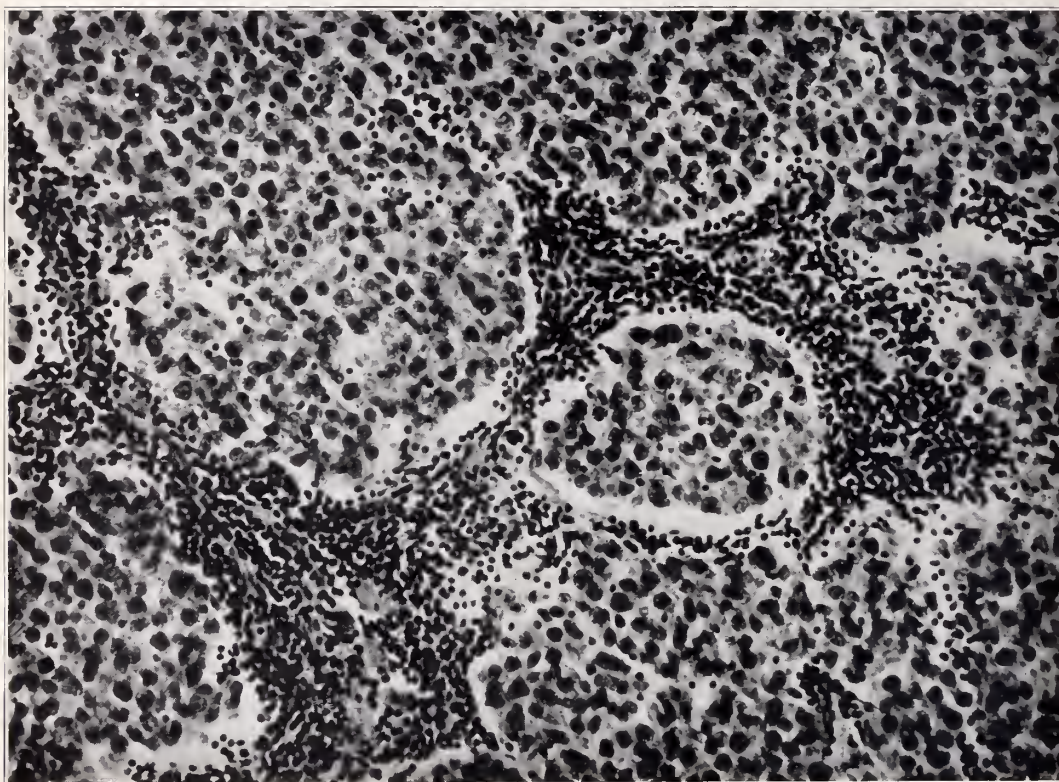


FIG. 27. Photomicrograph showing the typical histologic appearance of a pinealoma.

Infundibuloma: Recently, I have introduced a new name for a type of tumor which springs from the floor of the third ventricle. Such tumors resemble very closely in their vascular organization and cellular elements, the infundibulum, the lower end of the tuber cinereum (fig. 31). Hence the term *infundibuloma*. Little need be said about this rather rare type of tumor, beyond calling attention to the fact that it is usually incorporated in the floor of the third ventricle (figs. 32, 33), projecting into and often completely closing this cavity. Its removal is impossible without completely disrupting the floor of the third ventricle, an indis-

pensable structure. Thus, it must be regarded as malignant and beyond any measure of relief or cure.

Metastatic brain tumor: Little emphasis need be placed on the unpromising outlook for this form of brain tumor. It may be best simply to repeat what I had to say not long ago in discussing a paper by the well known neurosurgeon, Dr. Horrax, in which he attempted to formulate criteria for the selection of metas-

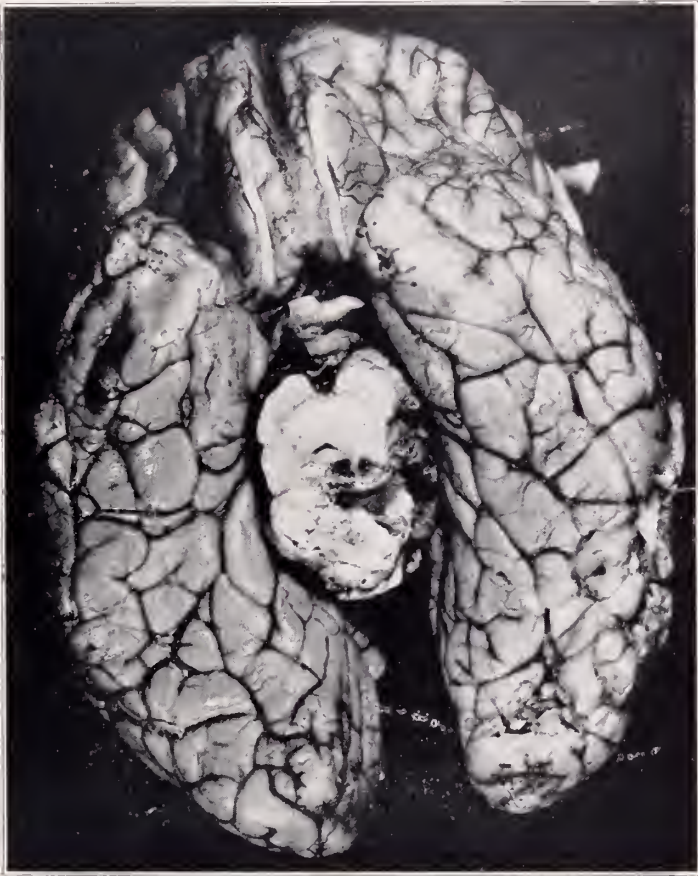


FIG. 28. The base of the brain showing the midbrain in cross section and the distortion and replacement of the quadrigeminal plate by the pinealoma shown in figure 27.

tatic brain tumors for successful surgical intervention. He believed to have accomplished this in about 10 per cent of metastatic brain tumors which he treated surgically as measured by the survival period of about two years.

A little over 20 years ago, in collaboration with Dr. Selinsky, I have investigated the problem concerning the clinical manifestations and behavior of metastatic brain tumor. We found, at that time, that there was a rather striking lack of satisfactory discussions on the subject of clinical and diagnostic features of

metastatic tumors of the brain. However, in the course of the past 20 years this subject has been enriched by many substantial contributions which have alerted the neurologist and neurosurgeon alike as to the prevalence of this type of intracranial expanding lesion as well as to the urgent need of recognizing it clinically before surgical intervention is decided upon. This most useful information was soon passed on to the internist and general practitioner, who most frequently serve as the source of clinical material for both neurologist and neurosurgeon. It is quite likely that this state of alertness is responsible for the great difference



FIG. 29. A large pinealoma seen overlying the quadrigeminal plate (tectum of the midbrain)

in the incidence of metastatic tumors as reported from different clinics. Dr. Horrax stated that among the 1,255 brain tumors which passed through his hands in the course of the last 10 years, 4.1 per cent were metastatic. This is in full accord with the incidence of metastatic tumors (4.2 per cent) found among the 2,000 cases of Cushing's collection. However, other reliable investigators have indicated different—mostly higher—figures. Walsche, for instance, found 6.4 per cent; Dandy gave a rough estimate of 10 per cent; Adson, on the other hand, encountered only two cases of metastatic carcinoma among 167 verified

brain tumors. In contrast to the aforementioned statistics I have reported in 1942 a series of metastatic tumors and found that they represented 13.5 per cent of the total number of brain tumors that came to post mortem examination. This high incidence, as compared with those reported by previous investigators, demanded an explanation. I, therefore, began to search for one.

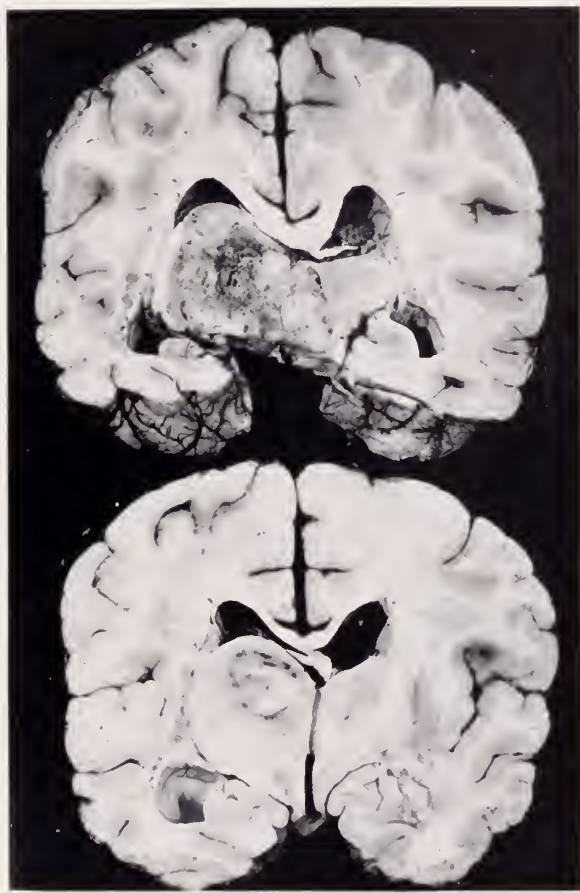


FIG. 30. Coronal section of a brain showing the invasive character of a pinealoma and its rostral extension into the brain tumor.

As I have already stated, my earlier calculations were based upon post mortem material. The thought occurred to me that a study of instances of brain tumors which have been verified surgically but did not come to post mortem would yield other figures. I have, therefore, taken 300 consecutive cases of surgically verified brain tumors and found an incidence of 12.6 per cent of metastatic lesions. But since these cases were those which were studied and treated on the free wards of the hospital, the question arose as to whether the cases of brain tumor treated in the private pavilion of the hospital would not yield a different propor-

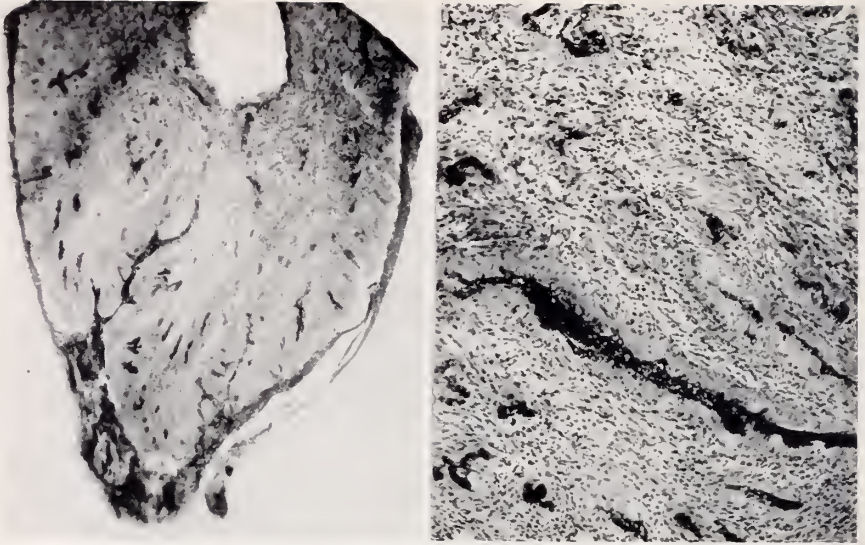


FIG. 31. A- photomicrograph illustrating the infundibulum in coronal section and B- showing its typical porto-hypophysial blood vessels.



FIG. 32. The base of a brain displaying the location and appearance of an infundibuloma.

tion of metastatic lesions. Ninety of such instances were analyzed and found to yield 9.3 per cent of metastatic lesions. It would seem that these observations suggest the looked for explanation. The growing accumulation of experience, providing better means for the discovery of the secondary character of an expanding intracranial lesion, and the increasing familiarity with the behavior of such tumors, have put the surgeon on guard against operative interference in instances of suspected metastatic tumors of the brain. This adds to the reduction of the total and the relative number of reported, verified metastatic tumors, while the

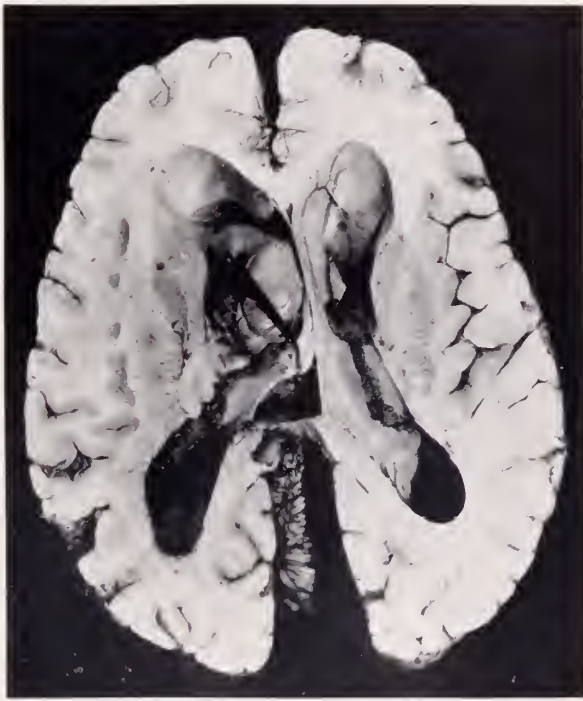


FIG. 33. The infundibuloma shown in figure 32 will be seen here herniating into the third ventricle blocking the foramen of Monro.

number of those verified by autopsy increases as permission for such investigation is more freely granted.

So much for the incidence of metastatic tumors. Now what about the criteria which would enable one to select cases in which surgical relief is of sufficient promise as to warrant such a step?

In full agreement with the observations of Horrax, there is the group of patients with previously known malignant disease, who show, in addition to the signs of intracranial involvement, evidence of systemic debilitation. They certainly fall into a category in which surgical intervention does not offer any promise of worthwhile extension of the survival period. It is equally true that patients with explosive onset and rapidly progressive course fall into the same

category. Another category, in which the onset is insidious, the course slowly progressive and signs of increased intracranial pressure are few and not too prominent, carries a little greater promise for a worthwhile salvage. But here other features, anatomical as well as clinical, so common to metastatic lesions must be borne in mind.

1. Metastatic tumors of the brain are in more than half of the cases multiple (fig. 34). In our general series it was estimated to be 52.6 and when we add to

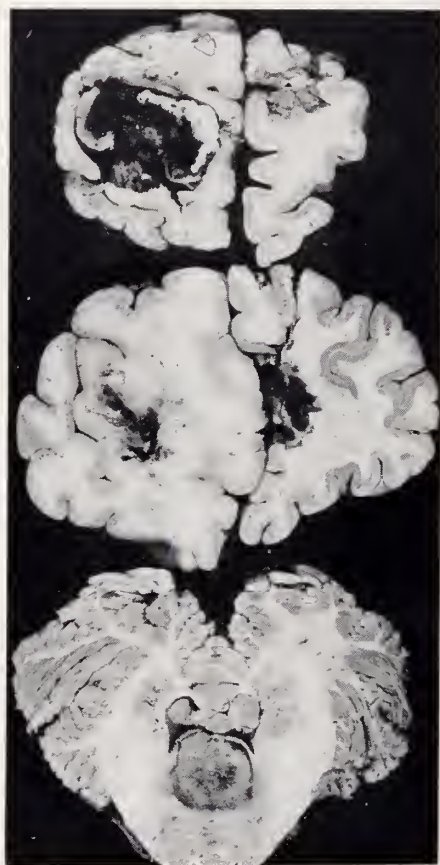


FIG. 34. Coronal section of a brain displaying the multiplicity of a metastatic carcinoma.

this group cases in which the lesion is widespread and diffuse the total percentage rises to 61. This percentage is a little higher with metastatic tumors which have their primary seat in the lung. The percentage here rises to 67.

2. The predominant number of cases of metastatic brain tumors have their source of origin in the respiratory tract (58 per cent). This is an obvious contraindication to surgical intervention.

3. In a great majority of cases studied at post mortem, the metastatic lesion or lesions in the brain are but an expression of a generalized process of dissemi-

nation of the malignant disease. It is to be borne in mind that in a very great number of instances the lung receives a metastatic lesion as part of this spreading process. Hence, the discovery of a shadow in a chest plate must not be accepted as indicating the lung to be the source of metastasis.

4. As already suggested, almost one-third of the metastatic brain tumors are single. However, this rather favorable condition must be considered in the light of the size and location of the lesion (fig. 35) and some of the indispensable functions of the brain that might be compromised by its presence or removal.

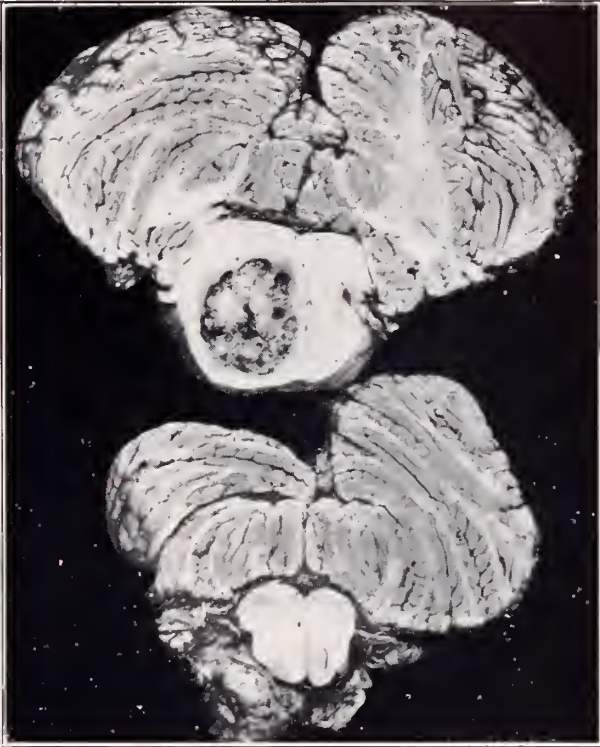


FIG. 35. Cross section of the pons exhibiting a single metastatic carcinoma.

It is obvious that all the aforesaid considerations narrow down the margin of safety for, and reduce the field from which, suitable cases may be selected for surgical intervention. This somewhat pessimistic conclusion should not in any way discourage further efforts to discover clinical means for the selection of cases in which surgical intervention might offer an extension of a comfortable, if not entirely useful life, bearing in mind that in some form of malignancy, as in hypernephroma, a single metastasis may be predicted with the lesion having such a location as to offer promise for its removal without resultant too serious a dysfunction, and with a survival period and a life sufficiently comfortable to justify such a step.

With the last subtopic dealing with metastatic brain tumors, the darker chapter of brain neoplasm may be considered closed—a somewhat happier outlook will be found in the following and closing discussion in which attention will be directed to two important categories: the pituitary adenoma and the meningioma.

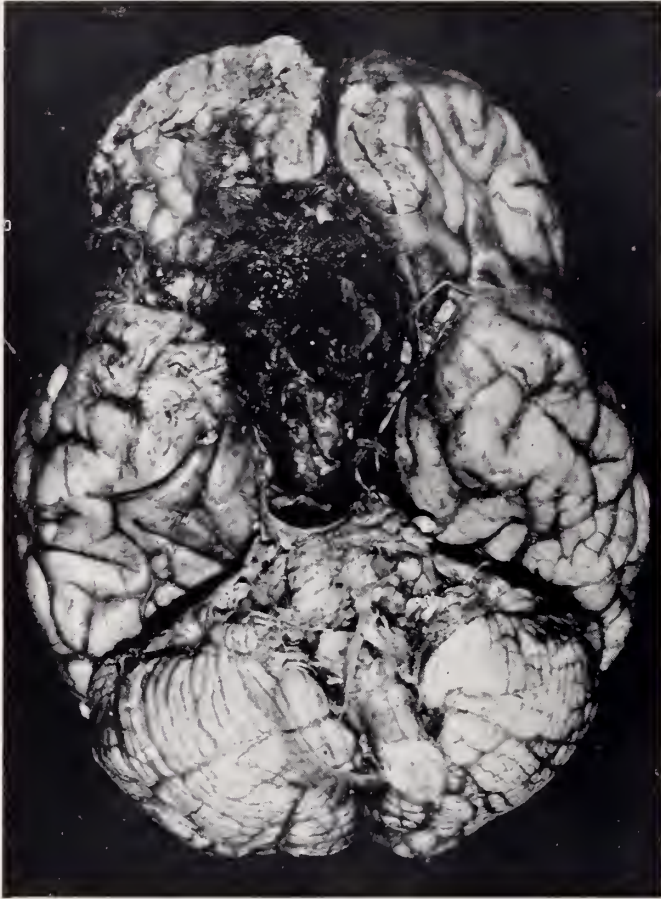


FIG. 36. The base of a brain showing the location, site and appearance of a pituitary adenoma.

Pituitary adenoma: One form of neoplasm related to the pituitary body was already considered when reference was made to craniopharyngioma. The form to be discussed under the name of pituitary adenoma is a primary neoplasm of the anterior lobe of the pituitary gland. It constitutes a large percentage of brain tumors and includes several variants: the chromophobic, chromophylic and the rare variety, the basophylic. These tumors have their primary seat in the sella turcica, causing enlargement, the thinning and erosion of its floors and of the clinoid processes. Not infrequently they acquire large size and break through the diaphragm sellae, encroaching upon the overlying structure at the floor of

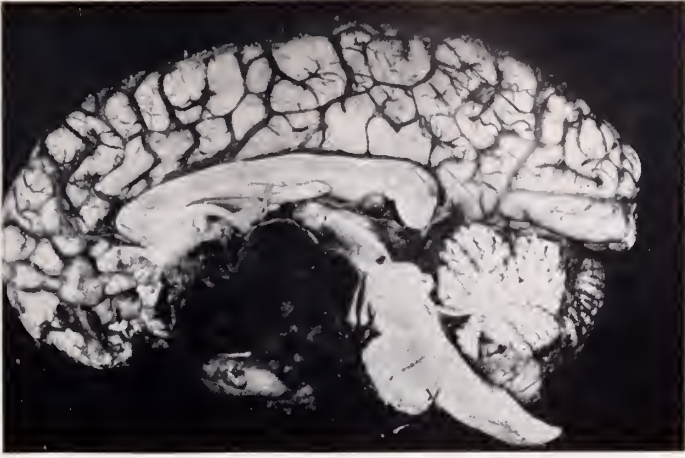


FIG. 37. Midsagittal section of a brain showing the disruption and distortion of the floor of the third ventricle by a pituitary adenoma.



FIG. 38. Photograph showing the appearance of a well demarcated meningioma in the frontal area of a cerebral hemisphere.

the third ventricle (fig. 36).⁵ In some such instances the tumor elevates the floor of the third ventricle to a point where the latter is reduced to a narrow slit (fig. 37), or else it breaks through this floor to invade the ventricle.

Thus, it is quite apparent that cases are not rare, in which the tumor though histologically benign, may through its location and its insinuation into the vital parts of the brain, become inaccessible and irremovable, and hence malignant in character. In some instances its histological character justifies its grouping with malignant tumors, carrying the threat of rapid growth, infiltration of the adjacent tissue and recurrence after partial surgical removal.

The neurosurgeon has had a rich experience with pituitary adenomas which were subjected by Cushing to a most careful study. In general, evidence is offered by competent investigators, based on a large material in support of the

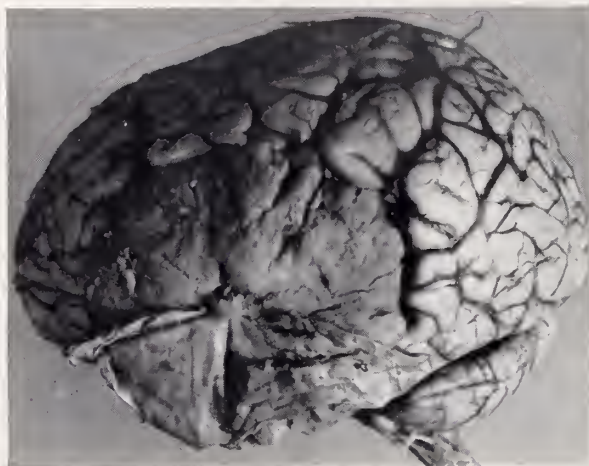


FIG. 39. A meningioma *en plaque* in the left cerebral hemisphere which by location and benign histologic character favors successful surgical intervention.

satisfactory experience in the treatment of these tumors, that either radiotherapy or surgery, or a combination of the two, are the only reliable therapeutic measures.

It is the consensus at present that pituitary tumors, when recognized early, should be treated with irradiation unless vision is dangerously threatened. When surgical intervention is found necessary it is carried out mainly to relieve pressure on the optic chiasm, and hence the removal is partial, for even if total removal were possible, it would carry with it the hazard of destruction of the pitu-

⁵ Dr. Ira Cohen was kind enough to read this article in manuscript and to make some constructive suggestions, which I quote with gratitude. With regard to the pituitary adenoma he said "I may be wrong, but I believe that most of these tumors break through the diaphragm sellae if they give rise to visual disturbances. Some few extend laterally to cause oculo-motor signs."

itary gland. There is ample clinical evidence that irradiation alone relieved pressure on the optic chiasm in an appreciable number of cases.



FIG. 40. The brain with the tumor shown in figure 39, removed, leaving only a shallow expression.

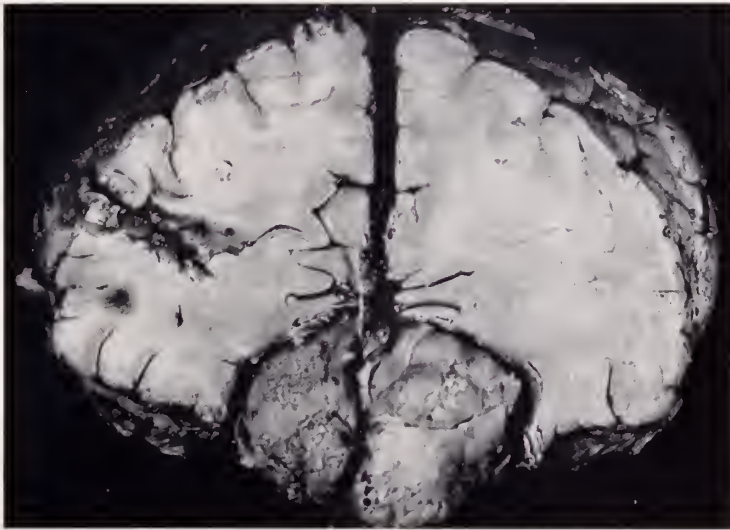


FIG. 41. A meningioma which grossly appears to be well demarcated and non-invasive (see figure 42).

Meningioma: The term, a fairly recent addition to the nomenclature, was introduced by Cushing some 25 years ago to replace the older term *dural endothelioma*. Other names were suggested but need not be discussed here.

The name, meningioma, suggests a tumor with its origin in an island of pri-

mordial tissue which is normally destined to become one or more layers of brain covering. There is good reason to assume that all of the four coverings of the brain: the pia, arachnoid, dura and bone have as their source of origin a single

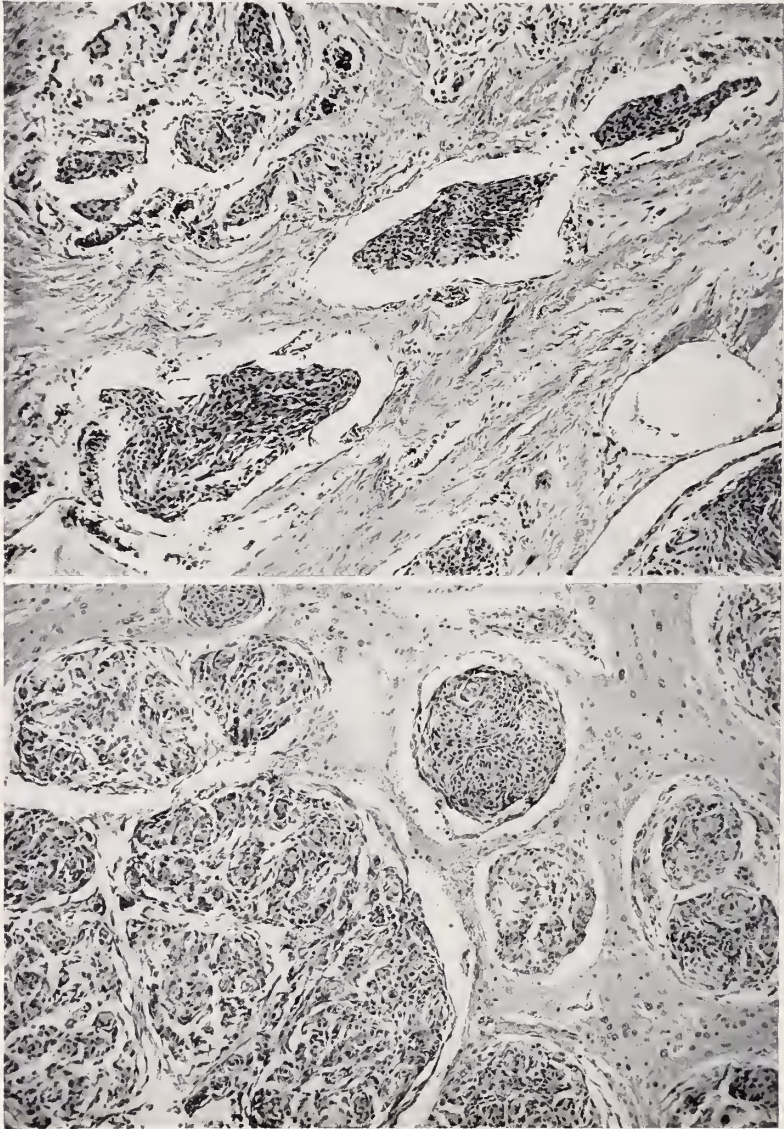


FIG. 42. Photomicrograph showing the invasive nature of the histologically benign meningioma shown in figure 41.

layer of mesenchyma which only covers the brain in its early phylogenetic and histogenetic stage of development. This mode of origin explains the numerous morphologic variants of the meningioma. The intimate relationship of the dura

to the brain substance explains why some of these tumors, consisting mainly of tissue *pial* in character, often infiltrate the brain tissue. The nature of the primor-



FIG. 43. Coronal section of a brain showing the gross appearance of a hemangiomatous or hemangio-endotheliomatous meningioma.

dial source explains also why some of them appear to spread in the overlying bone and why some retain an embryomal character and manifest features which justify their designation as sarcomas. Meningiomas which do not infiltrate the

subjacent brain tissue or those which do not fall into the category of sarcomas are many and may be regarded as benign, provided they are found in accessible locations (figs. 38, 39, 40). Even the slightly infiltrative lesions need not be re-

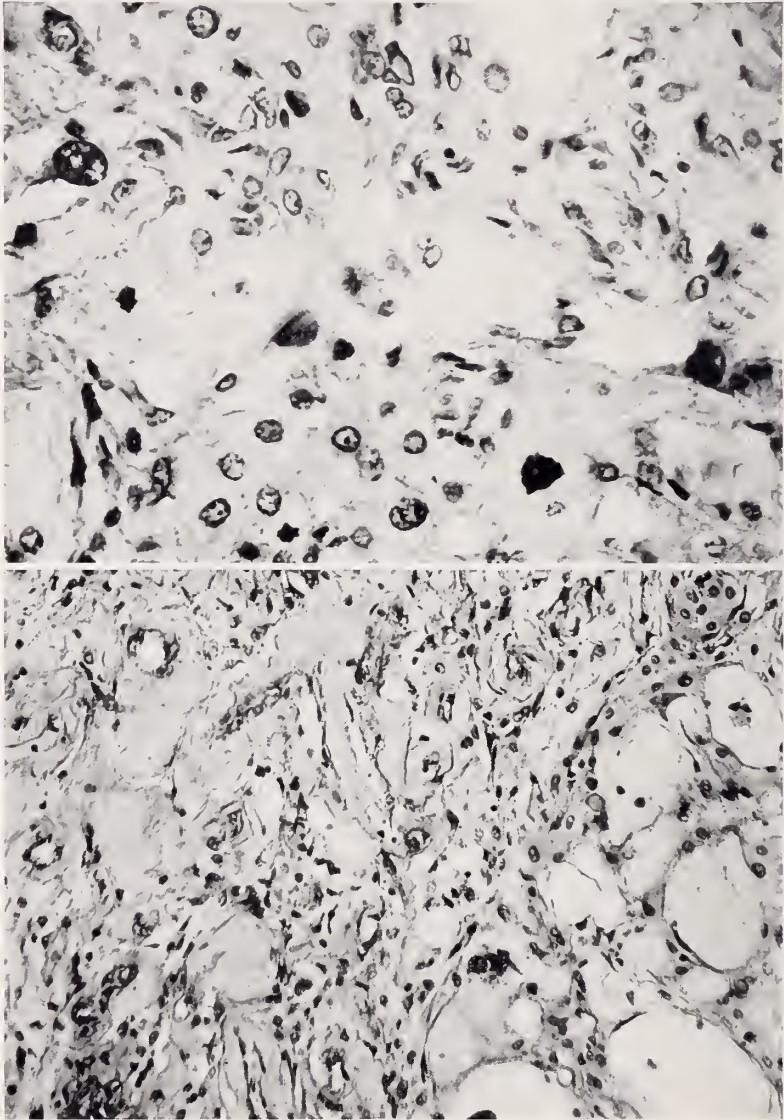


FIG. 44. Photomicrographs illustrating the histologic appearance of the tumor shown in figure 44.

garded as immediately malignant, for recurrence may be delayed here for many years (figs. 41, 42). The conclusion may be readily reached that many among the meningiomas fall into the category where surgery is indicated and holds out promise for relatively excellent immediate and remote results.

Hemangioma: Closely related to the meningiomas are the vascular tumors best designated as hemangiomatous meningioma (figs. 43, 44). These are variants of hemangiomatous growths which fall into several other categories, depending upon the type of vascular structure which dominates the histology of the tumor.

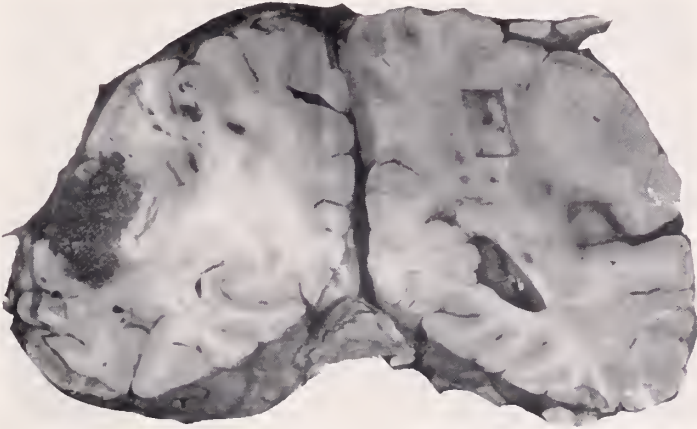


FIG. 45. Coronal section of a brain showing the appearance and location of a hemangioma (cavernoma).

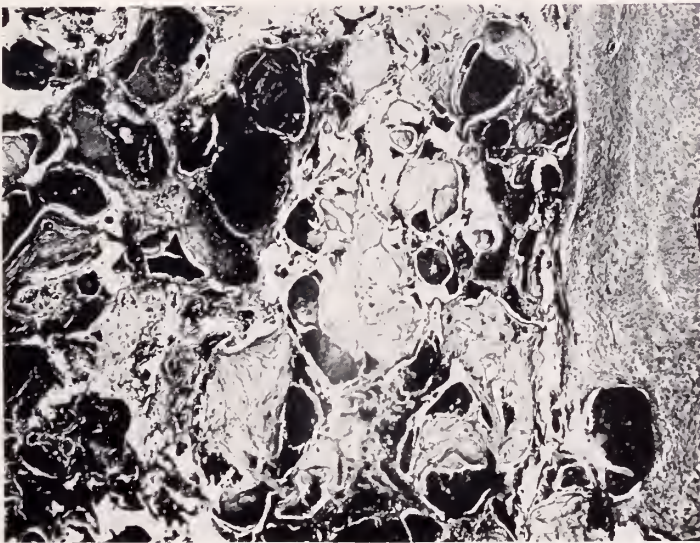


FIG. 46. Photomicrograph illustrating the histologic structure of the tumor shown in Figure 45.

Thus there are the so-called hemangioendothelioma, the sinusoid hemangioma, the capillary hemangioma and the cavernoma (figs. 45, 46). The developmental history of the vascular bed in the brain places these tumors in close relationship to the meningioma, and transitional forms linking these two large categories are found in the so-called hemangiomatous meningiomas.

Histologically, these tumors may be regarded as benign. In their location, in spite of the repeated statement that they all are usually located in the posterior fossa, they are equally divided between supra and infratentorial localization. With few exceptions they are accessible. The likelihood of spontaneous hemorrhage is, of course, a great hazard.⁶ Their diffusion into the substances of the brain occasionally makes their radical removal very difficult, if not impossible. This applies more frequently to those of supratentorial location. Those in infratentorial situation, occurring as they most often do, in the young and even in the child, are accessible and hold out good promise for thorough removal, which is often followed by a long and satisfactory survival period. They are often grouped with the astrocytoma, the reactive gliosis being erroneously interpreted, as the primary neoplastic process.

SUMMARY

In the foregoing an attempt was made to divest the subject of brain tumor of impressions still lingering from the heroic days of the Cushing and Dandy period.

Attention was directed to the histologic, histogenetic and gross anatomical features of brain tumors. It was indicated that in considering the benign or malignant character of such tumors it is necessary not only to investigate the inherent biologic qualities of the neoplasm, which ultimately determine the potency of the tumor for unrestricted growth, but also its accessibility for surgical intervention.

Attention was drawn to well documented data which point to the somewhat lengthened survival period in operative cases and to the exceptional instance in which a longer and useful survival period followed surgical intervention. These data, however, serve as a strong argument in favor of surgical restraint and greater co-operation between the neurosurgeon and the seasoned neurologist. Such joint function would insure against some avoidable errors and help in the selection of cases most promising for successful surgery.

With the foregoing in mind it was left to the mature reader to consider the importance of careful investigation of the individual case of brain tumor-suspect before a final decision is made in favor of surgical intervention. It follows that a thorough screening by a competent observer in the field is imperative to exclude such instances in which surgical intervention is but adding insult to injury.

My sincere thanks are due to Drs. Philip Bergman and Martin Green for their generous contribution of time and effort in assembling some of the statistical data used in this survey.

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⁶ The view is expressed by Dr. Ira Cohen that: "although we have seen bleeding (i.e. blood clots etc.) in some meningiomas, I do not consider this particularly hazardous. You may have correctly derived this conclusion from post mortem material".

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PHYSICAL SIGNS OF NUTRITIONAL DISTURBANCES

A REVIEW*

HERBERT POLLACK, M.D.

INTRODUCTION

The clinical diagnosis of nutritional states is dependent upon the development of standardized techniques. This implies the universal acceptance of the criteria of the normal as well as the abnormal. The point of departure of the abnormal must be defined, and much time will be necessary to accomplish this. The physical diagnosis of a patient is still mainly an art and not a science. The biological variations of the patient have yet to be statistically quantitated. When the variations of the patients are coupled with the variations of the observers, it is not surprising to find confusion in this field.

Means must be found to give the examiner a basis for recording the findings in purely objective terms; admittedly a difficult task. Errors in examination can be pointed out and eliminated. Physicians as a rule consciously or unconsciously compare a patient under observation with those he encountered before. For instance, one who has seen cases of beriberi in the Orient in its severe advanced forms is likely to disregard many patients who are diagnosed beriberi in this country. To him the latter are instances of minor conditions presenting no immediate threat to life as the Oriental form does. A practitioner from the South who is conversant with the classical forms of pellagra is not very often impressed with what is recognized as pellagra in the North.

In the course of training physicians in the art of nutritional survey work, certain situations soon become manifest. In the early experience of the neophyte, as he examines his first group of patients, he finds many abnormalities which correspond to the published descriptions of nutritional disorders. In time, as a number of patients with severe overt classical deficiency syndromes comes under his observation, he gradually begins to completely disregard all minor signs of nutritional disturbances, ignoring all but the classical ones. This tendency on the part of the physician to adopt an arbitrary grading of seriousness of the disorder is highly detrimental and must be avoided. Signs must be recorded in anatomical and precise terms. Their interpretations may vary as new facts are introduced. Thus anatomical descriptions are records which can be re-interpreted from time to time.

MASS SURVEY METHODS

Most of the methods for examining nutritional conditions have been devised to be applied to large groups of persons. Special examinations are designed to separate and rate the malnourished. The findings will vary in accordance with the following 4 general population groups:

* From The Metabolism Section of the Medical Services of The Mount Sinai Hospital, New York.

1. The so-called average, normal group, which is apparently well nourished.
2. Groups undergoing acute or chronic nutritive deprivation by famine or poverty.
3. The institutionalized groups confined in prisons and asylums; such individuals are fed from mass cooking without free choice of food; error in the planning of meals affects the whole confined population rather than family groups or individuals.
4. The so-called catabolic groups, or those with acute disease following injury, surgical intervention, or some other illness; this group is the one which most commonly shows acute nutritional deficiencies.

Before methods of examination of each individual within the group are outlined, it should be stated that the general appearance of the patient under investigation, since it is based upon impression, is not a reliable index.

The weight is an excellent index of the state of caloric balance when compared with the previously determined statistical standards. The latter must take cognizance of the race, color, nationality, of the individual under study. In mass surveys the height will automatically average itself. A body weight below average standard indicates an inadequate caloric intake for the activity, and the physical state of the patient.

It is obvious that to determine the nutritional status of a large population group, for reliable statistical data, a significant number of individuals must be examined. Signs presented may suggest but a single nutritional deficiency. Co-existent deficiencies of other nutrients may be present without gross clinical manifestations.

In a routine survey, there is little likelihood of finding the stigmata of complete lack of any one nutrient; there may be indications of a diminished intake only. It is necessary to discover the relative changes provoked by nutrient insufficiency rather than the signs of complete depletion. Under special conditions the more obvious manifestations of starvation and malnutrition will be recognized.

The examination is usually limited to a clinical estimate of the condition of the more readily accessible parts of the body, which lend themselves to comparatively simple observation. It is evident that such selected sites represent only guides to tissue changes which are occurring simultaneously all over the body. Apparent neglect of the other tissues is only a matter of necessity if not of convenience. The examination is usually centered on the following organs—

- a) the eye
- b) the tongue
- c) the gums
- d) the lips
- e) the skin
- f) the lower extremities
 - (1) reflex arcs
 - (2) dependent edema
 - (3) protopathic sensitivity (vibratory, or position, sense)

The interpretation of these pathologic indicators should be based upon a concept of dynamic changes rather than static conditions. The observer must bear in mind the specific tissue properties of growth and repair, and the degree and duration of nutrient deprivation, which lead up to the observed anatomical changes.

Time is a very important factor in the development of the observed anatomical and functional changes, for the rate of development of a tissue change will influence its gross alteration. In tissues subjected to an acute insufficiency of a specific nutrient, the changes immediately observed will be those which affect the more labile parts of the organ systems, such as the vascular bed; or the functional systems such as reflex activity or gastrointestinal motility.

Anatomical changes in such components as the epidermal layer of the skin, where conditions are more static, occur at a much slower rate. The syndrome of pellagra is a classical example of the time factor. To produce the thickened, scaling and pigmentation of the skin (from which the disease draws its name) requires a relatively long period of time. On the other hand, the tongue changes, stomatitis, and gastrointestinal manifestations can be precipitated within 24 hours under certain conditions. These are just as much a part of the disease syndrome as are the more obvious chronic skin changes. Their origin is probably related to the reactive vascular and nervous tissues and represents a more sensitive index to the lack of a specific vitamin.

Edema may be masked by dehydration. Inadequate salt intake or secondary acidosis from starvation ketosis are factors leading to dehydration. Latent edema may be exaggerated by the intake of an excess amount of fluid or salt. The deficiency edemas will then become overt only when conditions permit, even in the presence of prolonged calorie and protein starvation. In evaluating dependent edema, the time of the day is an important element which must be recorded. The late afternoon will show many more positive patients than in the morning. Local causes such as frostbite, trench foot, varicose veins, pregnancy, as well as systemic causes or cardiac dysfunction demand recognition. In the tropics, filariasis is a most common cause of lower extremity edema.

There is a specific relationship between nutrient requirements and total metabolic output. In extreme total emaciation, it is rare to see the stigmata of specific nutrient deficiencies. Such clinical syndromes as Simmonds' disease, anorexia nervosa, and Addison's disease are characterized by extreme tissue wasting. Pellagra, cheilosis, or beriberi are seldom found in this group of patients. Similarly, in starved population groups there is a low incidence of observed changes referable to the vitamin B deficiencies. The generally low metabolic level associated with starvation and certain endocrinopathies serves as a protection against specific nutrient deficiencies, as shown by the classical pigeon experiments. It was found that a diet consisting solely of polished rice will produce beriberi, whereas the fasting pigeon does not develop this disease. There must be some physiological basis for this difference. The function of the B vitamins in the body is coupled with the enzyme systems concerned with tissue metabolism. Decreased metabolism reduces the requirements for the enzymes; the need for their com-

ponent parts, the B vitamins, is likewise reduced. The danger in these cases is greatest during the period of nutritive rehabilitation. The sudden burden of increased metabolism, secondary to increased food intake, not infrequently precipitates acute manifestations of specific nutrient deficiencies.

Evidence is accumulating to show that there is a relationship between vitamin excretion and utilization, and the level and the kind of protein intake as well as the nitrogen balance. In catabolic patients or in patients with a negative nitrogen balance, certain oral lesions develop very often. The lesions resemble those of riboflavin, or niacin insufficiencies. Attempts to treat these lesions by the massive administration of niacin or riboflavin have frequently failed. This resulted in statements that these lesions were not vitamin deficiencies but manifestations of other reactions. It has been found, however, if enough protein of a high biological value is given with much smaller amounts of vitamins, these lesions rapidly disappear. Thus it seems that certain deficiency syndromes can be precipitated by an insufficient amount of vitamin in the presence of an adequate caloric and protein intake. On the other hand, these same lesions are produced in the presence of what might be considered an adequate vitamin intake but in the absence of a positive nitrogen balance. It is these concepts of inter-relationships that must be borne in mind when considering deficiency syndromes.

There are certain sites of predilection in which inadequacies of specific nutrients are first manifested by organic changes. Tissues are limited in their ability to react to irritants. The reactivity of a tissue is dependent, as previously stated, upon its component parts. For example, the gums consist of a multicellular layer (epithelium) and the blood vessels in a connective tissue stroma. With this histological concept a limited number of events in this tissue may be predicated:

- a. proliferation of vessels
- b. diminution in vessels
- c. dilatation or contraction of vessels
- d. hyperplasia of epithelial cells
- e. denudation of epithelial cells
- f. edema
- g. changes in the stroma
- h. infiltration by exudates

These alterations may cause change in color and size of the gums.

The observable color changes obviously can be the resultant of two main factors, (a) changes in the vascular bed, and (b) changes in the transmissibility of light through the overlying epithelial layers. An increased redness of the gums may be due to either actual hyperemia, or thinning or loss of the epithelial covering exposing the underlying vascular bed. An apparent pallor in the gums may be secondary to a diminution in the size or number of vessels, or an increased opacity of the epithelial layers, obscuring the normal color. The foregoing points are brought out to caution against the dangers and pitfalls of incomplete observations on the tissues which lead to erroneous diagnoses. The same conditions hold for the tongue: increased opacity of the superficial layers or round cell infiltration which serves the same purpose can mask an intensive

hyperemia of the underlying tissues. Every effort, therefore, should be made when recording lesions to analyze the component parts. Inspection shows that the filiform papillae on the tongue tip are frequently atrophied, giving the smooth red appearance. A furred tongue due to hypertrophic filiform papillae may appear pale.

The functional deficits caused by the neuropathies are commonly measured by sensory alterations and deep tendon reflex changes. In the motor reflex responses it is necessary to consider two components, the nerve and muscle. The acceptance of the results of this test as a true indication of nerve changes is dependent on the presence of a functionally normal muscle. Thiamin is only one of the several factors responsible for maintaining nerves in good functional condition. Disease states, such as syphilis, residuals of anterior poliomyelitis, tumors, and trauma, by their effects on the spinal nerves are well known causes of reflex abnormalities. All conditions leading to changes in the nerves and muscles must be evaluated before interpreting reflex changes in terms of nutritional inadequacies.

Deep tendon reflexes may manifest either hyper-activity or hypo-activity. That these are both phenomena in the same cycle of alteration has been demonstrated. The initial phase of alteration in the reflex activity is a hyperirritability; as deterioration progresses, the activity diminishes, passing through the normal to the hypoactive, and eventually to complete obviation. Restoration apparently goes through the reverse of this course. One of the most striking changes in the deep tendon reflexes are the developments of inequalities and variabilities in the responses to percussion. When a tendon is hit by the percussion hammer, the first time, the response may be hyperactive. A second, third, and even fourth tap may produce only a minimal response. The next attempt to elicit the response may frequently bring forth a very active one, usually characterized by a prolonged latent period between tap and contraction. The order of response may at times be reversed. Inequalities between the two sides are usual findings during the early degenerations in B avitaminosis.

The designation of new or active, and old or long-standing, lesions anatomically can be used in survey work. The functional changes associated with the vitamin, especially thiamine, deficiencies, present still another problem. When a function is restored, there is no residual evidence of its previous alteration, detectable by the usual clinical methods of examination.

Lesions due to nutrient inadequacies are subject to a good deal of individual variation. For reasons not yet fully understood, they are practically all subject to spontaneous remissions. The term "spontaneous" recovery is wrongly used in this connection; a better and more descriptive term will have to await a fuller understanding of the process. Some of the factors involved in such remissions are likely to be related to an improved adequacy of the supply of nutrients for the conditions encountered. This is well demonstrated by riboflavin, a nutrient about which a great many facts have been accumulated. This substance is rapidly destroyed in the presence of strong light. The amount of sunlight to which an individual is exposed may determine in part, on this account, the riboflavin requirements. There is evidence that other conditioning factors can determine re-

quirements for nutrients. Acute pellagra, as an example, was reported to occur in individuals in the wake of a general anesthetic. Here the cause may be found in the known effect of the anesthetic on the liver, an important site for the metabolism and storage of niacin. The effect of work on thiamine requirements has been considered, as it is conceivable that an adequate thiamine intake under certain conditions of rest would not be sufficient to protect the organism under conditions of increased physical effort and higher metabolic output. Such factors as sunlight, rest, work, infection, anesthesia, and many others are known as conditioning factors. A more complete evaluation of the conditioning factors in determining minimal daily nutritive requirements is, of course, in order. In this regard, even such a familiar measure in the nutritive pattern as calories must be considered from a dynamic, rather than a fixed, point of view. For expediency, one may refer to the daily caloric requirements of the average individual; it is, however, an unwise habit.

What may appear to be an idiopathic spontaneous remission of a symptom can be explainable by a change of some conditioning factor of which the observer is not aware. Hence the necessity for minute meticulous recording and analysis of all factors in the hope of finding a common denominator.

EVALUATION

With the foregoing limitations in mind, and by the careful interpretation of the chosen criteria it is possible to estimate the nutritional status of population groups. No single sign should be relied upon as an indication of a lack of a specific nutrient. Two or more signs pointing independently to the same deficiency are necessary for a final evaluation of the nutritional status of an individual. The diagnosis of thiamine deficiency can only be made when symmetrical changes occur in more than one pair of reflex arcs, and/or calf tenderness is present and/or vibratory perception is markedly diminished or absent, or a beriberi heart is present. For the diagnosis of riboflavin deficiency, angular stomatitis accompanied by cheilosis and/or facial seborrhea and/or vascularization of the cornea and/or a magenta-colored tongue should be present. For niacin deficiencies, the presumptive diagnosis will rest upon color changes of the tongue plus filiform and fungiform papillary changes in all parts of the organ. As mentioned previously, skin changes in this deficiency are so slow in developing that unless a severe long-standing deficiency is encountered, these changes may often be absent. For the diagnosis of the vitamin A deficiencies, certain of the eye as well as the skin changes should be present.

When the terms niacin, riboflavin, thiamine, or A deficiency are used, each term is one of convenience, referring to the more prominent of the presenting lesions; it is not meant to imply that the specific lesion is caused by the lack of one particular vitamin.

CLINICAL CONSIDERATION

The Skin

Vitamin A deficiency is manifested in human beings by lesions found chiefly in the epithelial structures. The skin alterations are notorious for their slow de-

velopment and recession. Unlike the ocular manifestations, cutaneous eruptions occur in relatively young persons between the ages of 16 and 30 years. It is common among men, and 90 per cent of those showing the dermatosis have obvious ocular manifestations of Vitamin A deficiency. Mild forms of dermatosis are encountered, which resemble the more florid eruptions of advanced vitamin A deficiency and respond readily to treatment with Vitamin A preparations. The severe dermatoses are found in the same geographic distribution as the advanced ocular dysfunctions.

As a result of Vitamin A deficiency, the skin exhibits a characteristic histologic change reflected in its gross appearance. Prominent is the keratosis pilaris resulting in a dry, scaly skin. Spinous papules protrude at the sites of the hair follicles and pilosebaceous pores. The rough skin may also be conditioned by the metaplasia of the sweat duct epithelium. In this condition of follicular hyperkeratosis, pigmentation at the base of the follicle may be present in long-standing cases. In their earliest stage, the papules resemble "gooseflesh"; later, when fully developed, the conical-shaped lesions are rough, horny papules, symmetrically distributed on the arms and thighs; the abdomen, back and buttocks become involved in very late stages.

Absence of pigmentation in the presence of marked folliculosis can be interpreted as a progressing lesion, while the presence of many pigmented spots without central papules are indicative of a receding lesion, the papules having been sloughed off by healing in some areas. Under effective therapy, pigmentation eventually disappears without leaving permanent residua. The age and development of the lesions have to be estimated from their general appearance and the feel on palpation; there is a long time-lag in such skin lesions.

The term, xerotic skin, applies to the dry, scaly, crinkly skin sometimes akin to the "fishskin" of ichthyosis. A relationship to Vitamin A deficiency is claimed but has not been clearly demonstrated; most frequently it is of congenital origin.

Vitamin B Complex Deficiency. A dry scaling skin is often a sign of inadequate nutrition. Protein and/or B Complex starvation should be suspected when the pigmentation is found particularly over pressure points, in bilateral and symmetrical alignment. The lesions are commonly situated over the ischial tuberosity, acetabula, sacrum, and other bony prominences, with those of the face may show a chloasma type of pigmentation.

Riboflavinosis, early, manifests itself in the skin by an oiliness, greasy, flaky yellow scales, and an erythema. In the more extensive lesions, there are filoform formations of sebaceous material over the nose and malar regions. It needs be differentiated from adolescent acne. In the more advanced deficiency states, a butterfly distribution of seborrhea over the cheeks and nose must be differentiated from lupus erythematosus and acne rosacea.

Infections such as furunculosis, impetigo, sycosis barbae, have been attributed to effects of Vitamin A deprivation on the skin. The presence of these and similar states should not be evaluated without other signs of A deficiency. Acneiform eruptions of the face are probably not due to Vitamin A deficiency. There has been some evidence of its relationship to the B Complex. Certainly the sebaceous gland involvement and seborrheas have multiple etiological fac-

tors, among them metaplasia of the epithelium on an A basis and the diffuse effects of the B Complex, especially riboflavin.

The dermatitis of pellagra is very variable in character, distribution, and chronology. Usually starting as an acute erythema, developing into vesicles which in time break and result in crusting and desquamation. The deeply pigmented, scaling lesions—thickened, cracked, and fissured—are usually seen on the exposed portions of the wrists, neck and ankles. The distribution is quite characteristic and should lead one to suspect the cause. Mechanical trauma in the skin folds, under the breasts, and around the groin and scrotum, very often lead to eczematous changes.

Recent studies indicate that pellagra is one of avitaminosis, consisting chiefly in reduced supply or utilization of nicotinic acid, riboflavin, and thiamine. The most prominent signs of pellagra are stomatitis, dermatitis, mental changes, gastrointestinal upsets and generalized weakness. It occurs most commonly in people of poor economic status because of the greater food restrictions in this group.

Vitamin C deficiency. Among the lesions common to all types of purpura (hemorrhage in and beneath the skin and mucous membranes) are the petechiae and ecchymoses which may be widely distributed in the Vitamin C deficiencies. They are usually found at points of trauma, namely, over the skin of the upper arms, and shoulders. A blood dyscrasia must be ruled out as a cause before a nutritional deficit is accepted as a factor.

The Head

The hair is to be carefully examined first. Dry staring hair is frequently associated with general nutritional inadequacy. The face may show a cloasma type of pigmentation, as described above. The face, naso-labial fold, and the external ear are common sites for seborrhea and this serves as a clue for the early detection of ariboflavinosis dermatitis.

The Eye. Xerophthalmia, keratomalacia, and nyctalopia is a common manifestation of Vitamin A deficiencies. Keratitis is found in ariboflavinosis. The eye changes, therefore, are important indicators in the differentiation of these syndromes.

The conjunctiva is a comparatively thin membrane, being constantly renewed as the top layers of cells are washed away by tears; this is well demonstrated by microscopic examination of eye washings. The initial lesion occurs in the conjunctiva and is known as xerophthalmia. Later manifestations are the so-called Bitot spots, followed by ulcers, and finally by keratomalacia.

It is essential to inspect the conjunctivae for normal transparency and glistening. The loss of lustre, a diminished transmissibility of light, wrinkling of the surface, or pigmentation are of course significant alterations. Photophobia and lacrimation is a common and readily recognized dysfunction. The vascularity of the sclera may appear to have changed, with the increased density of the conjunctiva and loss of transmissibility of light. The scleral vessels are less prominent, and in the extreme state of emaciation are completely invisible; the sclera then has a porcelain-like appearance—bluish-white or faintly yellow in tinge.

This conjunctival change is definitely reversible, and is unquestionably related to extreme forms of emaciation. Its relationship to any one specific nutrient has not been established.

The general vascular hyperemia can be grossly recognized in the caruncle and may be associated with an edema of this part of the eye.

The Bitot spots are small areas where the tissue changes are most advanced; they are grossly perceptible elevations of characteristic yellowish color, located near the limbal area at the level of the equator.

The keratinization of the epithelium extends to the ducts of the tear glands. This results in a "dry" eye which is partially responsible for the ulcerations so commonly seen in the late stages of Vitamin A deficiency.

In the earlier stages of the nutritional inadequacies, most frequently that of riboflavin, there is a vascular infiltration at the limbus. The normal limbal plexus does not extend into the cornea but in the presence of these inadequacies, the limbal vessels grow out into the cornea. These changes are readily demonstrated by the slit-lamp. In advanced cases there is a loss of acuity of vision due to loss through the window.

Nyctalopia, or night blindness, has been considered as the result of Vitamin A deficiencies. However, there are other causes besides this nutritional deficit. A therapeutic trial for the reversibility of the night blindness by the administration of large amounts of Vitamin A is necessary to establish with certainty this causal relationship.

Amblyopia was seen in the Orient amongst American soldiers held prisoners by the Japanese. These men have suffered from severe malnutrition, being denied both sufficient calories and specific nutrients. This amblyopia was due to an actual optic nerve atrophy which was reversible in the early stages, but untreated, became permanent. It is reported that thiamine hydrochloride was able to arrest the progress of this condition, and even a good general diet accomplished the same. It is significant that in the American soldiers who had been prisoners of the German Army, and who were also subject to severe malnutrition, this type of amblyopia was not encountered. It can be postulated that the deficiency so effected the nutrition of the nerve that the almost universal presence of malaria and the specific dysenteries which were treated chemically produced degenerative changes in the nerves.

The Lips

The lips are a common site of anatomical changes associated with general or specific nutritional inadequacies. While the basic pathology is the same in the lesions, anterior or posterior, to the line of closure, the environmental differences produce the entirely different gross appearance. That portion of the lip anterior to the line of closure will react quite differently from the lip posterior to this line. In the latter, the epithelial deterioration results in a denudation of the surface which, because it is constantly bathed in saliva and kept warm, suffers no trauma. Consequently, the capillary bed stands out very sharply and the buccal surfaces take on the appearance of intense hyperemia.

Anterior to the line of closure, where the surface is subject to drying and

trauma, it becomes hard and cracks, acquiring the appearance of chapped lips. The surface is granulating, friable, and the underlying bed intensely hyperemic. This lesion is known as cheilosis. It can be simulated in the edentulous person with ill-fitting dentures, though usually only the angular lesions are seen and the area of hyperemia is very limited. If the lesions are extensive, permanent damage may result, leaving blotchy white scars on the lips. At the angles, linear cracks develop which radiate laterally; these open sores, known as perleche, may become secondarily infected to leave permanent scars. Also, fissures in this location, derived from other causes, may be confused with those due to riboflavin deficiency. Seborrhea of the nasolabial folds, eyelids, and outer canthus of the eye and ears are lesions frequently encountered in this condition.

The aforementioned type of lip lesion is considered by most nutritionists as being due to riboflavin insufficiency. But it is well known that in the presence of an adequate riboflavin intake, when the protein intake is inadequate and a protein catabolic state exists, these lesions will develop and can be cured only by the restoration of a positive nitrogen balance. This type of lesion develops frequently in a postoperative and otherwise convalescent patient even though the attending physician has been giving him adequate vitamins parenterally. This is a disturbing situation and leads to the erroneous conclusion that the patient does not respond to the specific medication, and a general skeptical attitude toward vitamin therapy then develops. Hence it must be emphasized that general nutritive rehabilitation including positive nitrogen balance and caloric balances the basis, and that specific vitamins serve only as supplements. Lesions of nutritional inadequacy in the human are rarely so specific that the administration of a synthetic vitamin will restore the tissue metabolism to normal.

The Tongue

There is probably no more disputed field of nutritional diagnosis than the interpretation of the observed changes in the tongue. The understanding of the tongue change is dependent upon a knowledge of its anatomical structure and above all upon a thorough inspection of this organ. In examining the tongue the light must be good, daylight being preferable; cross lights, because of the added reflections from the moist surfaces will obscure some of the detail. The subject should be instructed in projecting his tongue to have its tip extend beyond the lower lip. The tongue must then be relaxed and allowed to rest on the lower lip. Tightly contracted muscles will produce local blanching and abnormal hyperemia. When the tongue is relaxed, a wooden spatula or tongue blade is drawn over the dorsum, starting at the posterior end moving it anteriorly to the tip. This direction is against the grain of the filiform papillae. A tongue may appear smooth at first glance and may suggest an atrophic appearance. This is not infrequently due to pressure against the hard palate or artificial dentures. Ruffling the filiform papillae will reveal the true status of their growth and the color of the underlying tissue. True atrophy of the filiform papillae will not infrequently give the appearance of hypertrophy of the fungiform papillae due to the recession of the tissue at the base. Conversely, hypertrophic fungiform papillae may be masked by the

filiform if they are not brushed aside. The habit of reporting tissue changes on the basis of individual components will result in better diagnostic acumen. The use of a hand lens is recommended. The binocular microscope is invaluable in detecting changes not apparent to the naked eye.

The observed color is dependent on the visibility of the underlying blood vessels, the extent of hyperemia, and the thickness of the overlying tissues which allow the transmission of the light. The tongue being a highly vascular organ is subject to rapid and marked color changes. When the filiform papillae are desquamated, the tongue loses its normally present white opaque coating and the underlying color of the muscle becomes visible. Hasty examiners will consider the tongue hyperemic or excessively red when in actuality the color is normal. On the other hand, there may be an intense hyperemia and congestion of the tongue muscles giving rise to a thickened edematous organ. But if the filiform papillae are hypertrophied, the redness and swelling is not readily recognized and the tongue is usually described as pale and furry. In reality, it is only its coating and not the tongue itself that is responsible for erroneous observation. Thus, thoroughness in examination calls for a systematic exploration of each part independently.

Specifically, the color changes independent of melanin type of pigment and local pigmentation from chemicals or medication, vary from the pale, smooth, atrophic tongue to the beefy-red, thick, edematous tongue. In classical pellagra, there is usually a denudation or atrophy of the filiform papillae, a hyperemia and edema of the muscular part of the tongue and a hyperatrophy and hyperemia of the fungiform papillae. This is known as the beef-red tongue or beefy-red glossitis.

The same tongue change is not infrequently seen in aforementioned protein catabolic states. In pellagra, where the deficiency is due in a major part, but not entirely, to the niacin and protein intake, there is a specific but incomplete response to the vitamin. In the catabolic and convalescent states, when the vitamin intake may be high but where the deficiency is in calories and protein, the response to therapy is only good when the latter deficiencies are removed.

It is important to recognize that these tongue changes are nutritional, usually of multiple origin, and that good general nutritional rehabilitation is indicated rather than specific vitamins by parenteral administration.

The scarlet red glossitis is accompanied by a subjective sense of soreness or burning of the tongue, or mouth. The edema of the tongue is manifested by the serrated margins which are accentuations of the tooth indentations. Ulcerations of the tongue and mucous membranes of the oral cavity may follow. These usually start as bullous lesions which break and become secondarily infected, forming flat, discrete, grayish ulcers. Specific therapy gives rapid relief when the lesions are due to nutritional inadequacies. In the riboflavin insufficiencies, the tongue has a peculiar purplish magenta color not unlike a mild cyanosis. The filiform papillae are rarely abnormal, but the fungiform papillae may be hypertrophied and hyperemic.

The differential diagnosis in niacin deficiencies presents a most difficult prob-

lem. One may not see severe acute or severe chronic niacin deficiencies when surveying ambulatory or working groups of the population. In rapid clinical surveys, the inferential diagnosis of niacin, or whole B Complex, deficiencies should not be made unless there is actual atrophy of the filiform papillae over an area beyond the tongue tip in addition to the fungiform changes previously described.

The Gums

The gums are subject to changes in vitamin deficiencies. They have generally been considered in association with Vitamin C. It has been pointed out already that these lesions lack specificity. Until there is a clarification of the mechanism of these gingival changes for survey purposes, it is recommended that they be used as an index of general, rather than specific, nutrient deficiency.

Gingivitis is universally seen, so much so, that it is difficult to describe the normal state. Normal gums are light pink in color closely adherent to the teeth. The interdental papillae are delta-shaped extensions between each of the teeth. The earliest changes in the gum are usually seen as a serrated line about 1 mm. below the dental margins. This is a hyperemic change and is manifested by a purplish color. Such a gingival line is not infrequently seen in conjunction with B vitamin insufficiencies. The intradental papillae are next affected, usually being swollen and hyperemic. If the edema is marked, the intradental papillae have a smooth, satiny, glossy and pale appearance. In the hyperemic phase, the purplish red color is the significant change. As the process extends, there is a separation of the gum margins which can be seen grossly or identified by the probe. When the margins separate, food is lodged between the gums and teeth, setting up an inflammatory reaction with an exudate. These inflammatory changes are easily recognized and differentiated from the acute scorbutic hemorrhagic gingivitis. This latter, once seen, with its spongy, friable, bleeding, ecchymotic appearance, cannot be confused with anything else except the acute gingivitis of leukemia.

There are many factors which contribute toward the formation of gingivitis. Among them are local trauma, malocclusion of the teeth, inadequate chewing, as well as nutritional inadequacies of both C and B vitamins. It is rather generally stated that Vitamin C deficiencies are responsible for the nutritional gingivitis, but not enough attention has been paid to the role played by B vitamins, particularly riboflavin and nicotinic acid, in this condition.

The estimation of Vitamin C deficiencies in working groups is crude at best. It is assumed that these workers, by virtue of the type of work they are doing, would have repeated episodes of superficial trauma. In the presence of a Vitamin C deficiency, even mild trauma may be expected to cause ecchymoses. If these subcutaneous hemorrhages are found, the subject should be investigated for signs of Vitamin C insufficiency.

A NOTE ON BERIBERI

Beriberi was only mentioned briefly in passing, therefore a more general discussion of the clinical findings of thiamine deficiency seems advisable. The classical beriberi is quite easily recognized by the circulatory, gastrointestinal, and

neurological changes. When present with edema, it is called the "wet form." In the dehydrated patients, it is known as the "dry form." Early objective signs are neurological in origin. There are quadriceps weakness, calf muscle tenderness and hyperesthesia of the feet. In the prison camps, this was known to the inmates as the "Happy Foot" or the "Burning Foot." From the subjective descriptions, it is a mixture of hyperesthesia and paresthesia. Vibratory sensation or protopathic sensitivity is lost and the deep tendon reflexes become altered.

Circulatory changes cause dyspnea, pulmonary edema, and in the wet form, anasarca. The heart failure is usually right-heart in origin. There is a tachycardia under exercise, but during sleep there may be a marked bradycardia. The response to thiamine is quite dramatic. If not treated, the result is tragic—sudden death is not uncommon. These cardiac and circulatory changes of beriberi differ from those of the starvation syndrome. In people who survive prolonged starvation there is a general muscular atrophy due to protein depletion. This muscular atrophy includes the heart muscle. The heart is small and atrophic in contrast to the enlarged heart of the beriberi. The blood pressure is low and the pulse rate may be as low as 30 beats per minute at rest. Under exercise or excitement, tachycardia sets in.

In states of total emaciation the secondary sex characters in both male and female almost always are lost. In the female there is also added menstrual disturbances, with the menses ceasing by the end of the third month. The affected woman is nevertheless still capable of being impregnated. There is an atrophy of the breasts and vulva. The face, arms, and legs develop hirsutis. In the male, the beard becomes soft and fuzzy; the penis is flaccid and shrunken and the testicles atrophy. Libido is lost very rapidly and impotence is common. Gynecomastia is seen in the male, not uncommonly in the early period of starvation. Signs of specific nutritional deficiencies may occur during the degredation phase, but are very uncommon in the late phase.

A NOTE ON NUTRITIONAL ANEMIAS

The term is restricted to the anemia resulting from insufficient dietary intake of iron. Anemias indirectly arising from other nutritional deficiency such as that which accompanies scurvy, pellagra, or hypoproteinemia are not included under this form. Indeed, this syndrome cannot be regarded as a clearly defined clinical entity. Certain normal physiologic moments such as pregnancy, pubescence, catamenia and the menopause materially alter the blood picture in so complex a manner that the definition of the norm for these special states is difficult to ascertain. In addition, other causes tend to confuse, such as chronic latent blood loss, local infection or tuberculosis, etc.

To recognize this state, it is necessary to obtain positive information through a dietary history. Local variations in the iron content of foods must be kept in mind. The symptoms are generalized and include lack of energy, headache, vertigo, dyspnea and palpitations. The condition is commonly accompanied by no distinct symptoms whatever.

Physical findings include pallor, loss of skin turgor, suboptimal weight and

reduced muscle tone. In advanced cases a soft apical systolic murmur may be heard and the pulse is rapid and of poor quality.

Most often, however, the diagnosis rests solely on laboratory findings. Because of limited information, the epidemiologist must surmise that in all probability nutritional anemia is of widespread, worldwide occurrence, and further extensive observations should be carried out in order to set up suitable public health and dietary practices to prevent this condition.

Nutritional anemias include both hypochromic and hyperchromic types. The iron deficiencies may be manifested by these hypochromic anemias in association with the spoon-shaped nails. Pernicious anemia, sprue, anemias of pregnancy, hypothyroidism, C deficiencies, are characterized by hyperchromic anemias. Thyroid and Vitamin C are specific for the anemias due to their inadequacies. Pernicious anemia, which is characterized by achlorhydria and leucopenia, responds to specific liver therapy or to vitamin B₁₂. The other hyperchromic anemias require folic acid for successful treatment.

CARCINO-SARCOMA OF THE UTERUS*

R. I. WALTER, M.D. AND N. MINTZ, M.D.

There occasionally arises in the uterus a single tumor possessing malignant epithelial and mesodermal elements in juxtaposition. Various theories have been advanced as to the histogenesis of these tumors. Virchow (1) considered them to be primary carcinoma or sarcoma in which the stromal or epithelial elements respectively were stimulated to malignant growth and called them carcino-sarcoma. Herxheimer (2) believed that the primary growth was carcinoma with secondary stimulation of the stroma to sarcomatous growth and called such tumors carcinoma-sarcomatodes. Meyer (3) considered some of these tumors to be the result of combined and mutual invasion of two independent primary growths (carcinoma and sarcoma) and called such neoplasms collision tumors.

The aforementioned theories of the "dual origin" of carcino-sarcoma were denied by several authorities (Ewing [4], Herzog [5], and Karsner [6]) who were of the opinion that carcino-sarcoma is primarily a carcinoma in which the epithelial cells due to vagaries of growth have morphologically changed into sarcoma-like cells. In a recent communication Saphir and Vass (7), in a review of the literature, have analyzed 36 reported cases of carcino-sarcoma. They concluded that all of these reported cases could be classified as primary carcinoma in which certain of the epithelial elements, by a process of metaplasia induced by chronic inflammation, x-ray, or other irritating factors, become transformed into spindle cells closely resembling true sarcoma.

Because of the rarity of these tumors the following two cases are reported.

CASE REPORTS

Case 1. (Admission # 431571). History. The patient, a woman aged 49 years was a gravida 2, para 2. She entered the hospital complaining of intermittent vaginal bleeding, leukorrhea, supra-pubic and back pain, and slight loss of weight. These symptoms had been present for a period of six months. Six years prior to admission this patient had received an unknown quantity of x-ray to the pelvis for the treatment of fibroids.

Pelvic examination revealed an uninfamed introitus showing moderate atrophic changes. A small fragment of necrotic clay colored tissue was protruding from the cervical os. The cervix merged directly with an asymmetrical nodular uterus transversely enlarged to the size of a 12 weeks pregnancy and reaching about 3 fingers below the umbilicus. The adnexa could not be differentiated from the uterine mass.

Course. On the day of admission the patient spontaneously passed a necrotic polypoid mass of densely cellular tissue measuring approximately 5 x 3 x 3 cm. Histologic study revealed it to be what was considered a primary myosarcoma with conspicuous glandular proliferation possibly carcino-sarcoma.

An exploratory laparotomy was performed. The peritoneal cavity contained approximately 500 c.c. of serosanguinous fluid. The uterus was enlarged to the size of a 6 weeks gravidity, the myometrium was friable and grossly invaded by a neoplastic process. The

* From the Gynecological Service and the Laboratory of Pathology, The Mount Sinai Hospital, New York, N. Y.

vesico-uterine fold of the peritoneum was also thickened and infiltrated. Both ovaries were enlarged four or five times the normal size and presented papillary growths on the surface.

The excised specimen was found to be an enlarged uterus measuring 6 x 5 x 5 cm. A greyish-white tumor nodule was present on the serosal surface. The myometrium contained a small intramural fibroid. The endometrial cavity was distorted and measured 5 cm. in length. The endometrium was thin and smooth except for a disc shaped cellular polyp arising from the left cornual region of the uterus. Another small polyp arose by a delicate pedicle from the lower margin of this polyp. Each ovary measured 6 x 5 x 3 cm. and exhibited several tumor nodules on the surface. When sectioned each ovary contained multiple small cystic areas filled with serous and glairy fluid. Figure 1 illustrates the appearance of the myometrium and a polyp under low magnification. Under higher magnification there are recognized numerous invading, carcinomatous glands (fig. 2) surrounded by sarcoma-like stroma containing large spindle shaped cells, multinucleated vacuolated cells, and many mitotic figures (fig. 3). The sarcoma-like changes in the stroma were chiefly limited to the stroma



FIG. 1. (Case 1.) Section of the myometrium and polyp

of the polyp as indicated in Figure 1 by the increased cellularity of the polyp. The ink line in Figure 1 shows the limitation of this process. However, in other, scattered areas in the myometrium there were similar stromal changes in the proximity of carcinomatous glands. Section of each ovary showed the presence of bilateral adenocarcinoma which was probably metastatic. The stroma surrounding the carcinomatous glands in the ovary were considered as normal (fig. 4).

Case 2. (Admission #465509). History. A woman, aged 64 years, gravida 4, para 4, complained of vaginal bleeding for a period of 9 months. Nineteen years earlier, because of persistent menorrhagia, she was said to have a fibroid tumor of the uterus. Operation was advised but she refused and the menorrhagia persisted until the onset of her menopause 10 years ago. From then until the onset of her more recent illness she had no vaginal bleeding. In February, 1940, 9 months before admission, she noticed the recurrence of bleeding which was moderate in amount but persistent. Curettage was performed at another hospital; no evidence of malignancy was discovered, but she was given a series of 32 x-ray treat-

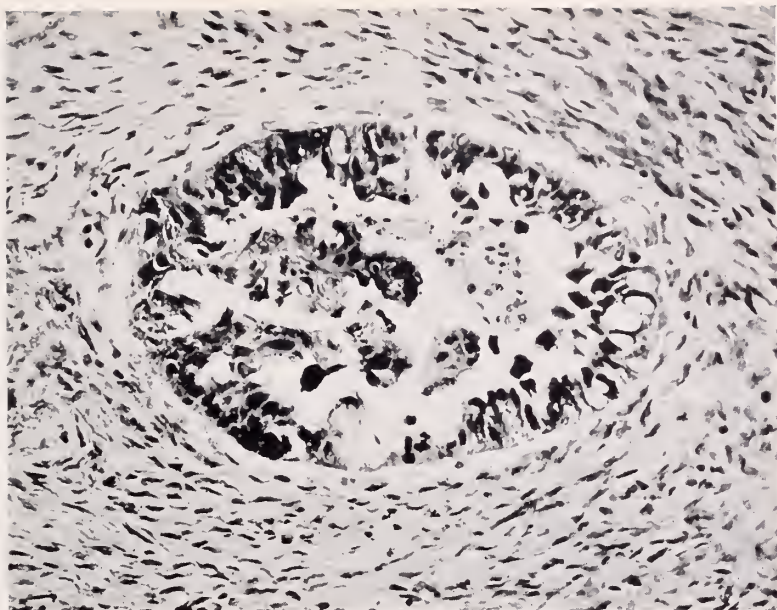


FIG. 2. (*Case 1.*) Section showing invading adenocarcinoma surrounded by cellular stroma, under higher magnification.

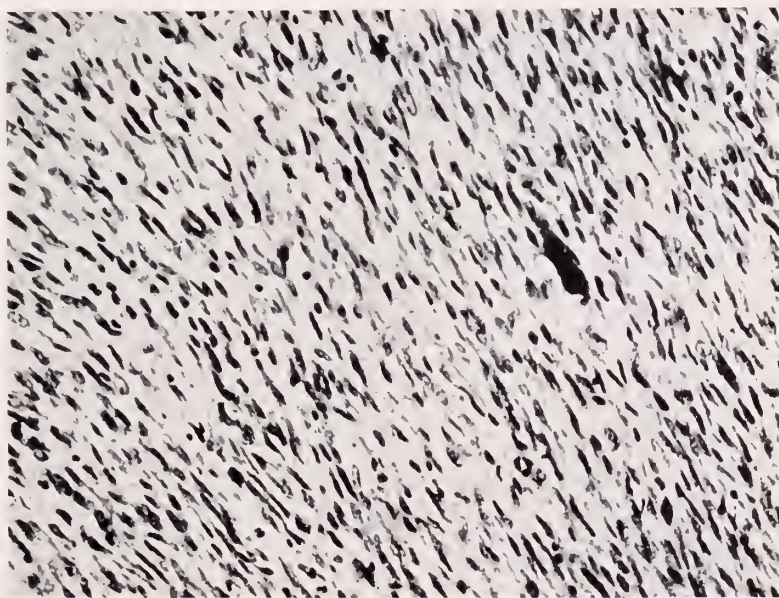


FIG. 3. (*Case 1.*) Sarcomatous stroma, multinucleated vacuolated cells, and mitotic figures, under higher magnification.

ments without effect on the bleeding. She soon began to manifest signs of anemia, and she became aware of a sensation of weight in the pelvis and developed symptoms of urinary urgency, dysuria, and nocturia.

Examination. On admission the patient appeared pale but well-nourished. The abdomen was slightly distended, and there was a large, firm, irregular mass occupying the lower abdomen and extending midway to the umbilicus. The external genitalia were normal. There was a trickle of blood issuing from the cervical canal. The uterus was irregularly enlarged to the size of a $3\frac{1}{2}$ months gravidity, smooth, and moderately movable. The adnexae were not separately palpable. Blood studies showed a hemoglobin of 45 per cent, and a red blood cell count of 2,600,000 per cubic millimeter.

Course. An exploratory laparotomy was performed. The uterus was found to be soft and symmetrically enlarged to the size of a $3\frac{1}{2}$ months gestation. The adnexae were negative. There was no free fluid or metastases in the peritoneal cavity. Because of the patient's age, general physical condition, and anemia, it was decided to perform a supravaginal hysterectomy and bilateral salpingo-oophorectomy, rather than to subject her to the increased hazard of a total hysterectomy.

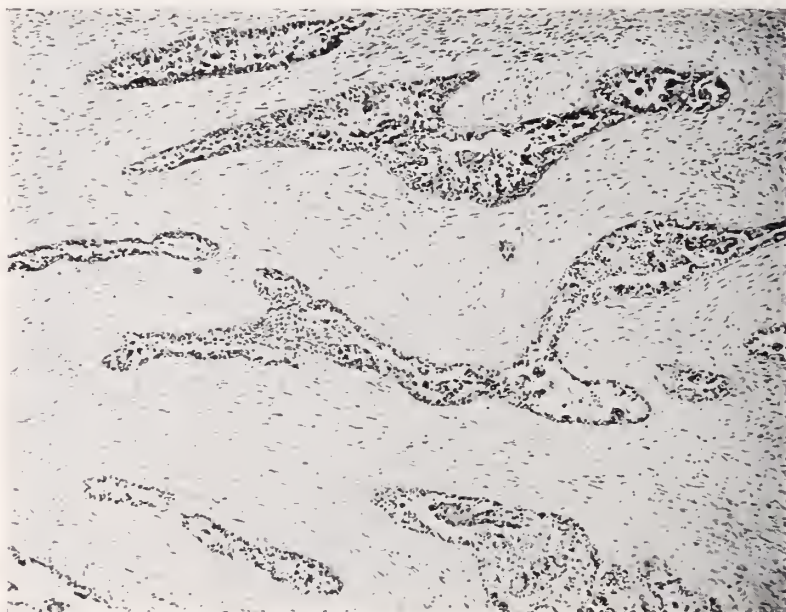


FIG. 4. (Case 1.) Metastatic adenocarcinoma of the ovary surrounded by normal stroma.

The excised specimen was described to consist of a supravaginally amputated uterus and both adnexae. The uterus was enlarged to the size of a $3\frac{1}{2}$ months gestation. The endometrial cavity was asymmetrical and measured 18 millimeters in length. Arising from the fundus and protruding into the endometrial cavity, there was a large sessile tumor, roughly oval in shape, and measuring 11 x 15 centimeters in diameter. The base of the tumor was sharply circumscribed, firm, and in some areas stony hard. In some areas the myometrium showed invasion by the neoplastic process for a varying distance. The endometrial surface of the tumor was nodular, yellowish-gray, and very vascular in some areas, and was covered by an irregular, firmly adherent, greenish-gray necrotic membrane. The cut surface of the tumor had a firm, fleshy appearance. The outer margin was reddish-pink for a distance of 1.4 centimeters into the depth of the tumor. The next area extending for a distance of 2.5 centimeters into the depth of the tumor was yellowish-white, firm, and honey-combed by numerous tiny cystic areas. The third and deepest layer of the tumor was bright yellow, poorly circumscribed, partially cystic, and in places calcified. In addition a degenerating fibroid tumor 8 to 10 centimeters in diameter was present in the myometrium beneath the

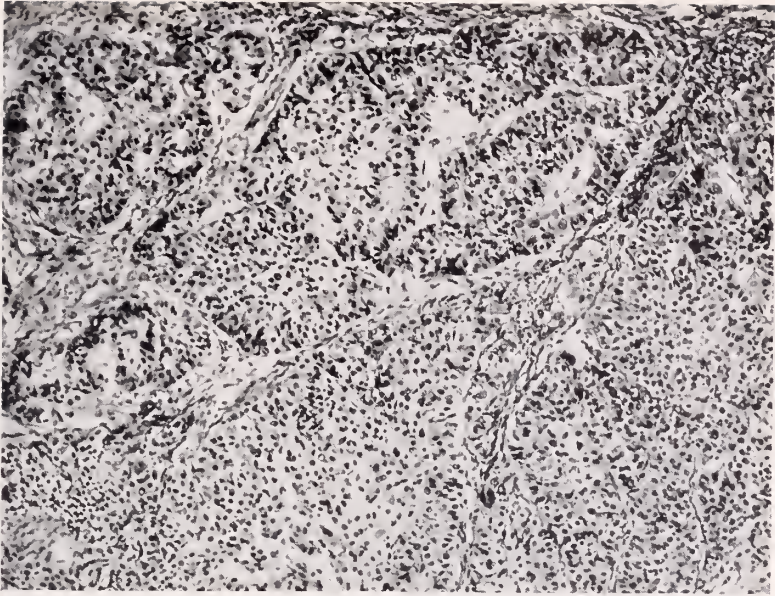


FIG. 5. (*Case 2.*) Section under medium power showing anaplastic adenocarcinoma of uterus.

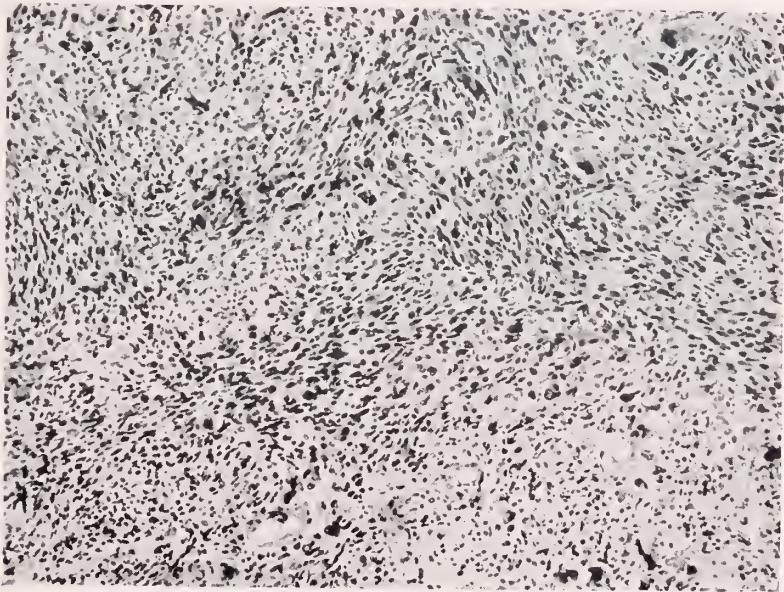


FIG. 6. (*Case 2.*) Stroma showing spindle-shaped hyperchromatic nuclei, mitotic figures, and occasional giant cell.

base of the endometrial tumor. The endometrial surface was smooth, glistening, reddish-pink, and extremely flattened, averaging about one to two millimeters in thickness. On the anterior wall there was a firm plaque-like thickening which was yellowish-gray in appear-

ance and on section was sharply limited to the surface of the endometrium. The tubes were normal and the ovaries showed senile changes.

The main portion of the large polypoid tumor projecting into the endometrial cavity showed an adenocarcinoma with a marked degree of anaplasia (fig. 5). In addition there were several areas of interlacing bands of fibrous tissue with spindle-shaped hyperchromatic nuclei, a few mitotic figures, and occasional giant cells (fig. 6). These areas were in apposition to areas of typical carcinoma. A silver stain (fig. 7) of this section revealed that the fibers ran parallel with the individual spindle-shaped cells, a characteristic that is commonly attributed to sarcoma. In another section was an isolated area of squamous cell metaplasia of the epithelium. Beneath the carcinoma there was a large fibromyoma which showed extensive necrosis and hyaline degeneration. Section through the endometrial plaque-like area revealed a typical adenocarcinoma with sparse glandular formation, invading the myometrium for a varying distance, closely resembling the larger tumor and apparently a metastasis therefrom. The myometrium otherwise showed no unusual features

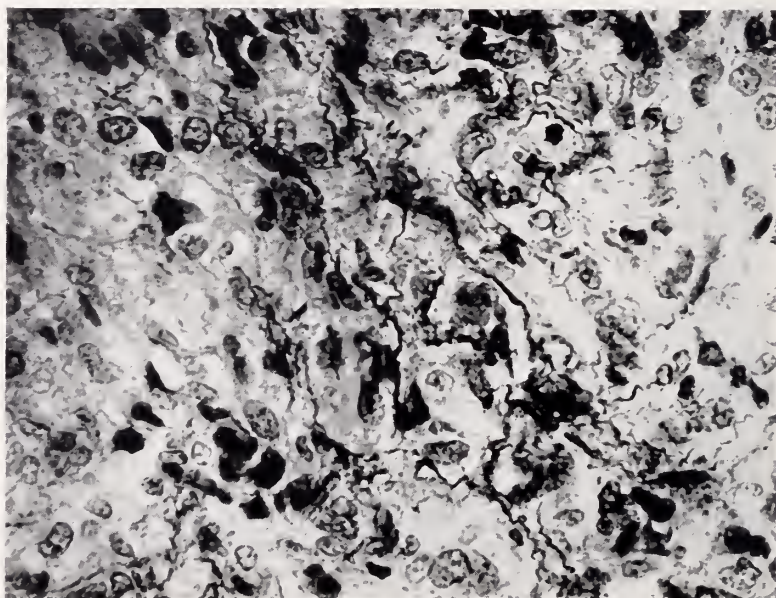


FIG. 7. (*Case 2.*) Silver stain (higher magnification) of section illustrated in Figure 6, showing that the fibers are parallel with the spindle-shaped cells, a characteristic commonly attributed to sarcoma.

Both ovaries showed considerable senile changes with marked atrophy. There was no evidence of metastases to the adnexae.

SUMMARY

Two polypoid tumors of the uterus which possess the morphologic appearance of carcinoma and sarcoma have been presented. In one case there were metastases to the ovary which histologically were carcinoma. In the second case, the endometrial metastases were similarly carcinomatous. Despite the failure of these tumors to metastasize as sarcomas, we are of the opinion, on the basis of the histologic findings alone, that they represent two separate tumors. The failure of the sarcomatous elements to metastasize may be the result of the relatively

low malignancy of the sarcoma as compared to the highly anaplastic carcinoma. It is noteworthy that the carcino-sarcoma in these cases, as well as in most of the reported cases, arose in endometrial polyps.

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STUDY OF RS-T SEGMENT CHANGES IN INDUCED CORONARY INSUFFICIENCY USING ESOPHAGEAL LEADS*

PRELIMINARY REPORT

J. WENER, M.D.,† L. SCHERLIS, M.D.,‡ A. A. SANDBERG, M.D., A. M. MASTER, M.D. AND A. GRISHMAN, M.D.

INTRODUCTION

Studies correlating electrocardiographic and anatomical findings in cases of acute coronary insufficiency have shown that the RS-T segment depressions, characteristically found in this condition are associated with subendocardial necrosis (1-3). Similarly the negative displacement of the RS-T segment in the standard limb and precordial leads in patients with coronary sclerosis after exercise (3) and after the breathing of 10% oxygen mixture (4) has been ascribed to transient anoxemia of the subendocardium. Experimentally induced injury to the subendocardial surface of the left ventricle has produced elevation of the RS-T segment in leads from within the cavity of the left ventricle (6-8), while epicardial leads taken directly over the damaged subendocardial areas have shown RS-T segment depression (5-8).

If the depression of the RS-T segment in the standard limb and precordial leads in acute coronary insufficiency is due to anoxemia localized mainly to the subendocardial aspect of the left ventricle, simultaneously recorded potentials from the left ventricular cavity should consistently show positive displacement of the RS-T segment. Esophageal electrocardiograms taken at a certain level of the left atrium have been shown to reflect left ventricular cavity potentials; leads taken below the atrial level usually record the potentials of the posterior surfaces of the heart (9).

In this study, therefore, esophageal leads in addition to the conventional standard and unipolar extremity and chest leads were utilized to investigate the nature of RS-T segment displacement in induced acute coronary insufficiency.

Methods: Simultaneous esophageal, standard and unipolar extremity and precordial leads were recorded in patients with angina pectoris, before and immediately after the 2-step exercise test (11). The esophageal electrode consisted of an ordinary duodenal rubber tube containing a central core of 15 separate fine wires, each of the latter being connected to a separate external metal band spaced at 1.75 cms. apart.¹ This esophageal lead was inserted into the esophagus under fluoroscopic control with the tip of the catheter selectively placed 4 to 5 cms. below the diaphragm. All electrocardiograms were taken with the direct writing three channel Technicon Electrocardiograph.

* From the Cardiographic Department and the Cardio-Vascular Research Group, The Mount Sinai Hospital, N. Y., N. Y.

† Fellow of the Dazian Foundation for Medical Research.

‡ Trainee of the National Heart Institute, U. S. Public Health Service.

¹ Made to our specification by C. R. Bard Inc., Summit, New Jersey.

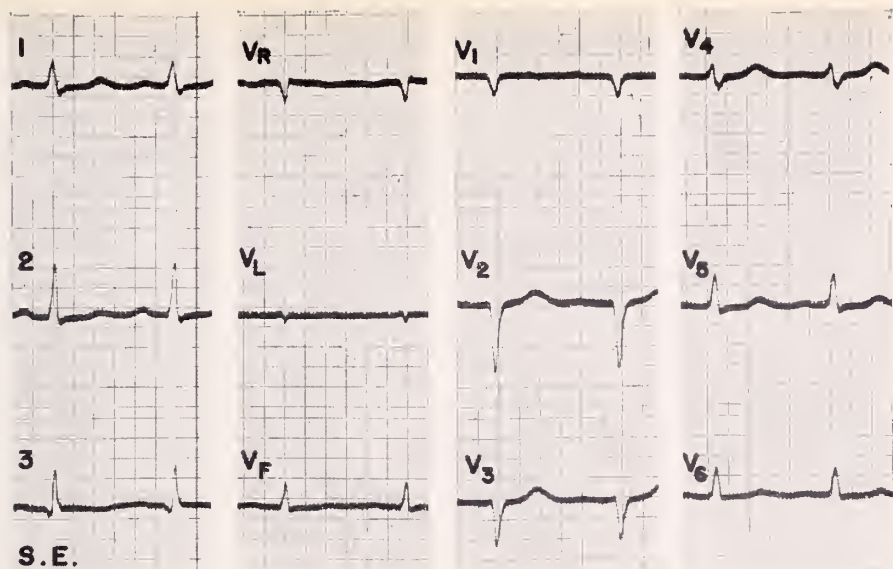


FIG. 1. S. E., male, 38 years of age, suffering from angina pectoris for the past one and one-half years. The conventional electrocardiogram is normal. (Leads 1, 2 and 3; V-1, V-2 and V-3 taken at 10 mm/MV; VR, VL and VF at 15 mm/1 MV).

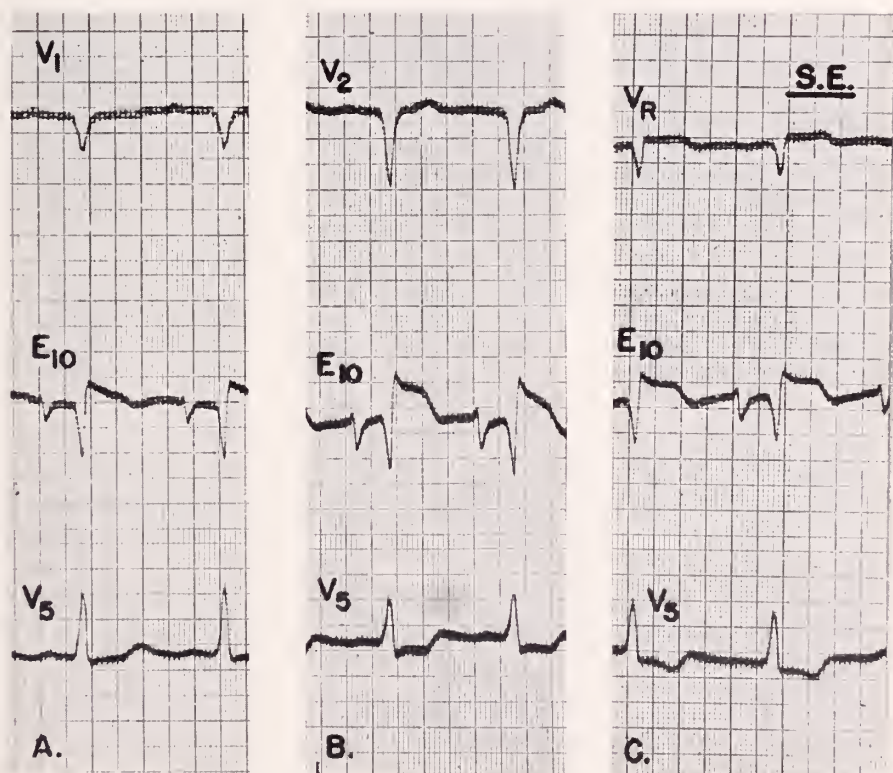


FIG. 2. E-10: Esophageal lead at atrial level reflecting left ventricular cavity potential.
 A. Prior to exercise, immediately after passing esophageal electrode: RS-T in V-5 slightly depressed, slightly elevated in E-10.
 B. Immediately after exercise: Marked RS-T segment depression in V-5 and elevation in E-10.
 C. Five minutes after exercise RS-T segment less elevated in E-10. Note elevation of RS-T segment in VR.

Results: In patients with angina pectoris, the depressions of the RS-T segment recorded in the standard limb and precordial leads immediately after exercise were regularly associated with elevations of the RS-T segment in the esophageal leads taken simultaneously at atrial levels reflecting left ventricular cavity potentials (Fig. 1). More pronounced depressions of the RS-T segment were at times recorded in the esophageal electrocardiograms which reflected the posterior surfaces of the left ventricle. Inversion or flattening of the T waves in the precordial leads after exercise was associated with similar findings in the esophageal leads reflecting the posterior surface of the left ventricle. Simultaneously the T waves in the leads at the atrial level became positive following exercise, after having been negative before. Within 15 minutes after exercise the electrocardiograms were back to the resting record.

DISCUSSION

According to the concept of Wilson et al. (10) relating to myocardial injury, the pattern of electrocardiographic changes obtained after exercise strongly suggests predominant injury to the cells in the subendocardial layers of the heart, wherein the current of injury is directed mainly towards the left ventricular cavity. This is evidenced by positive displacement of the RS-T segment in esophageal leads reflecting left cavity potential and its negative displacement in the precordial leads. The RS-T segment depressions in the esophageal leads reflecting the posterior surfaces of the heart indicate that the changes to the subendocardial region of the heart produced after exercise are not localized but widespread in nature.

These preliminary observations, in accord with the view of others (3-4) indicate that in induced acute coronary insufficiency the myocardial changes due to anoxemia are mainly located in the subendocardial aspect of the heart.

Similar studies are being carried out to investigate the nature of the RS-T segment displacement in left ventricular hypertrophy and after the administration of digitalis.

CONCLUSIONS

1) The RS-T segment depressions in standard and precordial leads after exercise in patients with angina pectoris were consistently associated with elevations of the RS-T segment in simultaneously recorded esophageal leads reflecting the left ventricular cavity potentials.

2) These observations strongly suggest that the electrocardiographic changes induced by exercise are mainly due to transient injury of the subendocardial layers of the left ventricular myocardium.

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ELECTROCARDIOGRAPHIC CHANGES OF CORONARY INSUFFICIENCY DURING THE FORMATIVE STAGE OF CORONARY OCCLUSION

WITH A NOTE ON POSTERIOR LOCATION OF ANGINAL PAIN*

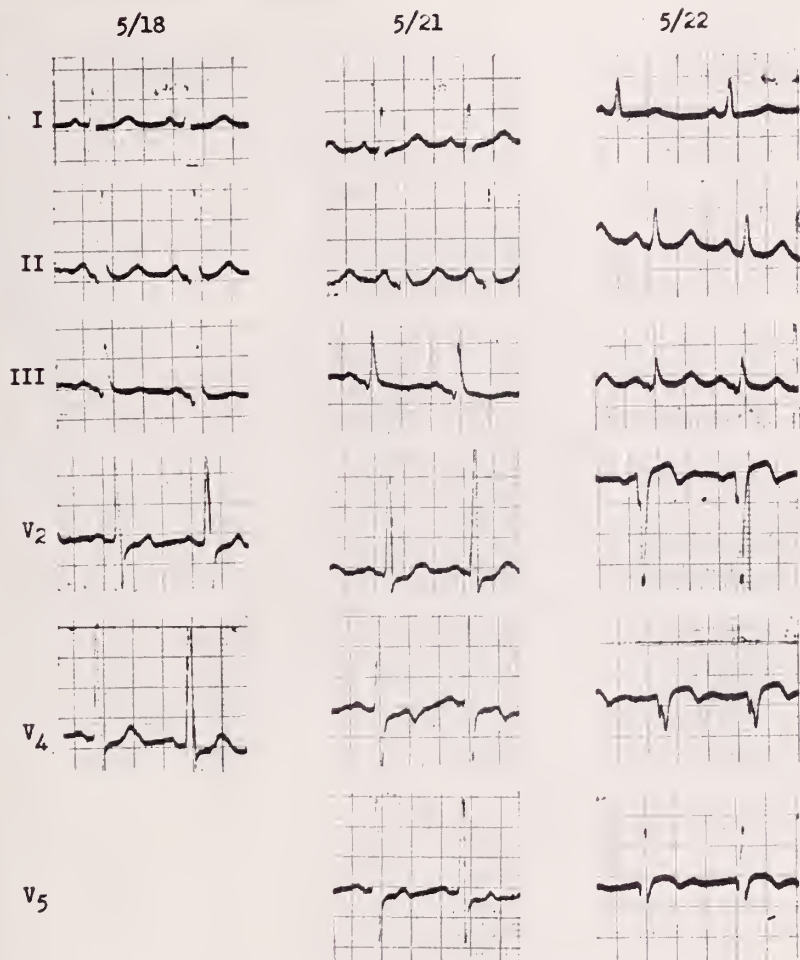
HARRY L. JAFFE, M.D.

Although the acute attack of coronary occlusion often sets in abruptly, the formation of the thrombus in the coronary artery is usually a more gradual process and may require a considerable period for completion (1, 2). During the premonitory phase the gradual encroachment of the lumen by the enlarging thrombus or subintimal hematoma may impede the flow of blood through the artery and produce progressive coronary insufficiency with myocardial ischemia or subendocardial necrosis (3). As a result, in approximately half the cases, the acute attack is preceded by symptoms of coronary insufficiency of varying severity (4, 5). Mild precordial pain, malaise, weakness or nausea may appear but more diagnostic is the abrupt onset of repeated anginal pain, at rest or on effort, or the sudden aggravation of a previous intermittent anginal syndrome (1, 6). Occasionally only a single anginal seizure precedes the acute attack, which may be delayed. The premonitory period of coronary occlusion usually lasts several hours or days but may be prolonged up to several months (1). During this phase evidence of myocardial infarction is usually wanting, e.g., tachycardia, gallop rhythm, drop in blood pressure, fever, leucocytosis and altered sedimentation rate. However, in occasional cases, one or more of these findings is present although the abnormality is usually slight. Thus, the degree of coronary insufficiency may be mild, producing only anginal pain, or may be sufficient to result in areas of necrosis in the subendocardial region.

It is accepted that RS-T elevation is associated with subpericardial involvement and that RS-T depression accompanies subendocardial ischemia or necrosis (7-9). We have pointed out that, because acute coronary occlusion usually produces through and through infarction, RS-T elevation and Q-waves appear in this condition, whereas coronary insufficiency is ordinarily associated with subendocardial necrosis and RS-T depressions (1, 3). During the premonitory phase of coronary occlusion the electrocardiogram is variable and reflects the degree of coronary insufficiency and subendocardial ischemia or necrosis present. The record may remain entirely normal or unchanged until the onset of the acute occlusion clinically (4, 5). This was formerly believed to be the rule but for some years we have observed an increasing number of cases with RS-T depression or T-wave inversion, the usual changes seen in coronary insufficiency, with or without subendocardial necrosis (1). These alterations may be slight and evanescent, and vary from lead to lead, or may persist for weeks until the occlusion is complete and the acute attack occurs. At that time the electrocardiogram is abruptly transformed into the characteristic pattern of massive, through

* From the Cardiographic Department, the Mount Sinai Hospital, New York.

and through infarction with Q-waves and RS-T elevation. Recently we have observed several exceptional cases in which transitory RS-T elevation was present during the premonitory phase of coronary occlusion spontaneously or after exercise (10). In these cases the coronary insufficiency was presumably severe



N.H., #565068, m. 45. RS-T depression and T-wave inversion in the chest leads, indicating coronary insufficiency, during the premonitory phase of coronary occlusion (5/18,21). Following the acute attack RS-T elevation and Q-waves appeared in leads V₂ and V₄ (5/22).

FIG. 1

enough to result in ischemia of the subpericardial region of the myocardium as well as the subendocardial. In rare instances the RS-T depression present during the premonitory stage persists for 12 to 24 hours following the acute occlusion, the RS-T elevation and Q-waves appearing thereafter (11).

CASE REPORT

History: N. H., #565068, a man, aged 45 years, a lawyer, by occupation, experienced severe pain at the base of the skull for the first time while walking to work. The pain lasted several minutes and was accompanied by profuse perspiration. A similar episode occurred the following day and three days later. He continued working without pain during the next three days before coming to the office for examination. He appeared well and physical examination was entirely normal. His blood pressure was 120/80. Fluoroscopy showed the heart to be normal in size and pulsation. The electrocardiogram showed slight RS-T depression in leads $V_{2,4}$. (fig. 1, 5/18). His temperature was normal. In spite of the atypical location of the pain and the minor nature of the electrocardiographic changes, a presumptive diagnosis of the premonitory phase of coronary occlusion was made and the patient was put to bed. He was relatively free of pain. An electrocardiogram taken in the afternoon of the third day in bed revealed an inverted T-wave in lead V_4 (fig. 1, 5/21), suggesting that some subendocardial necrosis had occurred. That evening, while in bed, he again experienced pain in the back of the neck associated with nausea and vomiting. It was excruciating and lasted four or five hours. Nitroglycerin did not afford relief. The next day the electrocardiogram showed the typical pattern of coronary occlusion with antero-septal infarction, i.e., leads V_2 and V_4 showed a large Q-wave and RS-T elevation (Fig. 1, 5/22). His course was uneventful and he was permitted out of bed after four weeks.

DISCUSSION

In this case the clinical and electrocardiographic findings point to the following sequence of events. A thrombus began to form in one of the left coronary branches either secondary to a subintimal hemorrhage or directly upon an intimal break. During the next week the thrombus gradually increased in size producing coronary insufficiency as evidenced by anginal pain at rest and RS-T depression and T-wave inversion. During this period foci of necrosis probably appeared in the subendocardial region. In spite of complete bed-rest the thrombus continued to grow until on the tenth day the artery was completely occluded resulting in a through and through infarct and RS-T elevation and Q-waves. Another explanation of this change, but one which is much less frequent, is that the infarction gradually spread to the subepicardial region, as the coronary insufficiency increased, without the formation of a complete occlusion.

It must be emphasized that, while the sudden onset of a recurrent anginal syndrome often is the harbinger of a coronary occlusion, as in the case here reported, the subsequent course of such a patient may be quite different. 1) The anginal pain may gradually subside after several days or weeks or, occasionally, similar episodes may recur during the following few months and then subside, without the development of an acute attack. During this period the electrocardiogram may be normal or show RS-T depression and T-wave inversion typical of coronary insufficiency. If the changes persist for a week or more or laboratory evidence of infarction appears, subendocardial necrosis is present. The initial arterial changes in these cases are probably similar to those present in cases which go on to occlusion, i.e., subintimal hemorrhage or an accelerated phase of coronary sclerosis, but thereafter a thrombus does not form at all, or it fails to grow sufficiently to occlude the lumen, or it grows so slowly that sufficient collateral circulation is able to appear and prevent acute infarction when the occlusion is complete. In favor of the latter possibility we have observed several patients who experienced anginal pain for several weeks during which time only

T-wave inversions were present. Then the pain ceased and the electrocardiogram returned to normal. A diagnosis of coronary insufficiency with subendocardial necrosis was made; yet a routine tracing taken four to six months later, the patients having been free of attacks, revealed the typical QT pattern of through and through infarction which had occurred insidiously. 2) The severe anginal pain may continue for a number of months. Although the attacks may increase in severity, there is no major episode suggesting acute coronary occlusion and the electrocardiogram is normal or presents only RS-T depression or T-wave inversion of varying degree. During this period there may not be evidence of subendocardial necrosis. Although such patients may gradually recover, as do those in the preceding group, the majority finally succumb. In two recent patients with such a history necropsy revealed markedly narrowed coronary arteries and complete infarction of the left ventricle but no acute occlusion. The RS-T was depressed in the electrocardiogram. In other cases, as one might expect from the extent of the infarction, the electrocardiogram reveals Q-waves and RS-T elevation. The association of through and through infarction with coronary insufficiency, rather than thrombosis, is rare but it brings up the possibility that, in cases such as the one reported in this paper, the change from RS-T depression at first to RS-T elevation later on results from the spread of the infarct to the pericardial region on the basis of coronary insufficiency without the formation of an acute occlusion. However, we think such a sequence of events is much less common.

The sudden occurrence of one or more attacks of coronary pain, particularly at rest, is always suggestive of acute changes in the coronary arteries and myocardium and deserves thorough investigation (1, 6). Although the pain may appear to be merely an episode of angina pectoris, that is, a temporary functional disturbance, an electrocardiogram may reveal Q-waves and RS-T elevation indicating acute coronary occlusion. Even if the electrocardiogram is normal, but the pain is severe or recurrent, the patient should be put to bed since subintimal hemorrhage or other changes may have occurred which may go on to thrombosis or infarction or both. Several tracings should be taken and if RS-T depression or T-wave inversions appear and persist for a week or more it is likely that subendocardial necrosis has already occurred. Thereafter the patient should be followed to determine whether the process will stop or go on to coronary occlusion and through and through infarction.

The use of heparin or dicumarol during the premonitory phase of coronary occlusion was suggested by us in a previous paper in order to prevent completion of the occlusion (1). A theoretical objection to such a procedure is the possibility of increasing the tendency to subintimal hemorrhage in cases in which that is the initiating mechanism of the occlusion. This danger would seem slight. In any case, it would be difficult to evaluate the effect of these drugs in preventing occlusion since it is impossible to foretell, in a case in which the formative stage of occlusion is suspected, whether the process would subside spontaneously or go on to complete occlusion.

The recognition of atypical locations of coronary pain is of considerable practical application. The case reported was remarkable because the pain was ex-

perienced only in the back of the neck, a fact which prompted a physician to make a diagnosis of spondylitis and to omit consideration of coronary pain. Although it is well known that anginal pain may radiate from the anterior chest posteriorly to the scapular region, and in our experience such radiation is very common, it is not recognized that coronary pain may be situated only or chiefly posteriorly, with some radiation anteriorly. It is distinctly rare for the pain to be confined to the back of the neck but its relation to effort in the present case pointed to its origin in the heart. No local cause, e.g., spondylitis, for the atypical location was found.

CONCLUSIONS

The sudden onset or aggravation of an anginal syndrome usually indicates recent changes in a coronary artery with acute coronary insufficiency. Subendocardial necrosis is often present. The process may progress to acute coronary occlusion and through and through infarction.

During the premonitory phase of coronary occlusion the electrocardiogram may present 1) no change and may remain normal; 2) RS-T depression or T-wave inversion or both, the changes of coronary insufficiency with or without necrosis; 3) in rare cases RS-T elevation which is transitory.

Occasionally the RS-T depression present during the premonitory stage persists for a short time following the acute occlusion.

Coronary pain is often situated in the posterior chest and may be limited to the back of the neck.

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Anesthesia in Surgery of the Patent Ductus Arteriosus. M. H. ADELMAN. *Anesthesiology*, January, 1948.

A study is presented of 30 cases of patent ductus arteriosus in which ligation was performed. The pertinent physical findings and hemodynamic derangements in these patients and a brief description of the operative procedure are reviewed. The problems of fluid therapy and anesthetic management are discussed. The average candidate for surgical ligation of the patent ductus arteriosus is a good anesthetic risk and offers few anesthetic problems. The satisfactory physical status of these patients, their normal lung parenchyma, the absence of cardiac and pulmonary manipulations and the freedom from untoward operative respiratory and circulatory reflexes simplify the anesthetic management. The only major anesthetic problem is one common to all open chest surgery, the prevention of pulmonary decompensation.

Multiple Simultaneous Acute Putrid Lung Abscesses. A. H. AUFSES. *Dis. of Chest*, 14: 41, Jan./Feb., 1948.

Acute putrid lung abscess usually occurs as a single lesion. In the subacute or chronic stage the infection may spread via the bronchial tree and secondary abscesses may develop. The simultaneous appearance of multiple acute putrid lung abscesses is a rare clinical occurrence. A case is reported in which 3 distinctly separate acute putrid lung abscesses appeared within a week of the onset of symptoms. The etiological factor was aspiration of infected particulate matter from the mouth. Each abscess behaved differently—one perforated, causing a localized putrid pyopneumothorax which was drained; another disappeared spontaneously, and the third was treated by surgical drainage. A complete cure was obtained.

Technic and Problems of Roentgen Ray Epilation. H. T. BEHRMAN AND F. C. COMBES. *Arch. Dermat. & Syph.*, 57: 74, January, 1948.

One of the major problems confronting physicians during the war years was the epidemic of ringworm of the scalp. This disease of children below the age of puberty has always been a serious menace to public health all over the world during the period of a major war and its accompanying devastation. The reasons for its spread to epidemic proportions during such periods are primarily lack of parental observation and control, as well as uncleanness. The epidemic which occurred in this country during the last decade began with a few scattered and sporadic cases in various cities and gradually fanned out to involve the entire country. At the height of the epidemic, as many as 1,000 new cases a year were encountered in the active clinics of medical institutions. Diagnostic and treatment centers were established in strategic areas throughout the country. Information relevant to early diagnosis, case finding and treatment was widely disseminated. The public health aspect was stressed, and both nursing and medical units worked in close cooperation

throughout the national school system. Rural as well as urban centers had their periodic scalp examinations by physicians skilled in the diagnosis of this disease. With the passage of time, the epidemic has been brought under control because of the combined efforts of dermatologists and public health authorities. At the same time, plans have been evolved to minimize the recurrence of future epidemics of this type. Various new drugs have been employed with success in certain types of ringworm of the scalp, but the major weapon of control in the so-called "human" type of case is roentgen ray therapy.

This article deals with the technical problems of roentgen ray epilation and measures for control of the disease.

Structural Patterns of Callus in Fractures of the Long Bones. With Reference to Healing after Internal Fixation. E. M. BICK. J. Bone & Joint Surg., 30: 1111, January, 1948.

The pattern of the external or primary callus of any fracture of the long bone represents the most economical structure which will serve as a rigid line of transmission for the stresses and strains normal to that bone in its long axis. This will hold until such time as osseous continuity through the fracture line has been restored by the internal or definitive callus. The quantitative distribution of the mass about the shaft will be conditioned solely by the mechanical requirements of the displaced fragments, and by no other factor. The single apparent exception is not actually an exception. The pattern of the primary callus following internal fixation does follow this same rule but the conditioning factor; i.e. the displacement, has been altered by the internal fixation, and the fixative, be it screw or bone plate, serves the function of the primary callus.

Psychosomatic Medicine in Daily Practice. BENNETT W. BILLOW. Am. Practitioner, 2: 321, January, 1948.

With the view of ascertaining the important role and frequency of psychosomatic disease in the average daily practice, the author has studied the records of 300 cases chosen at random, 150 from the year 1941 and 150 from the year 1946. The following data from the records were obtained: A working diagnosis after the first visit; the most common complaints and those diagnosed as functional; sex of patients; those diagnosed as functional were further questioned as to whether they had seen other physicians prior to their visit, and the name of medication, if received; a recheck and re-evaluation of the functional diagnosis of the 69 patients seen in 1941 after a lapse of 5 years. A routine first visit consisted of a history taken by the author which included chief complaint, family history and personal history. Under personal history, information was elicited about childhood, adolescence, sex, marital and physical life of the patient. Physical examination included routine urine analysis, blood count and fluoroscopy. Subsequently, additional laboratory steps were employed and the advice of consultants was sought. The most common complaints among those diagnosed as psychosomatic cases were (a) weakness, fatigue, tiredness, "no pep"; (b) nervousness, tenseness; (c) insomnia; (d) headaches; (e) lack of appetite, lack of breath, lack of air (sighing), sticking heart pain; (f) sensation of lump or pressure in chest or throat. Contrary to popular belief, the writer found no evidence that the female sex was more neurotic. Among the 300 unselected patients, 140, or 47 per cent were diagnosed as functional. Another 30 to 35 per cent of the patients, in whom organic disease was found, presented symptoms far out of proportion to the physical findings. Thus, since approximately 70 to 75 per cent of the patients examined have psychosomatic complaints, the importance of this problem cannot be overemphasized. It is stressed that most of the psychosomatic patients have been previously seen by from 1 to 4 other physicians. These patients constantly complained of having been told that they were "nervous." Their problem was not fully understood, and psychotherapy was not employed. Phenobarbital tablets had been administered to practically all of the patients. Patients must be made aware that their complaints are due to their emotional disturbances. The physician should be on the alert for evidences of disturbance of the psyche. A re-evaluation of the functional diagnoses of the 69 patients seen in 1941 after a lapse of 5 years, reveals that the writer erred in but 1 case and questionably in another. A brief history of 2 cases is presented.

Blood Volume Determination. M. MENDLOWITZ. Bull. U. S. Army M. Dept., 8: 58, January, 1948.

Blood volume determinations on normal subjects were performed with the cell dilution method. In this method the blood volume is calculated from hematocrit determinations before and after infusion of 600 cc. of plasma. The results were satisfactory and indicated that the method might be useful in the treatment of shock.

Repeated Gastro-duodenal Hemorrhages without Discoverable Explanation. BURRILL B. CROWN. Gastro-enterol., 10: 120, January, 1948.

This is a study of 120 cases of gastro-duodenal hemorrhage. Approximately 80 per cent were explainable on the basis of gastric or mostly duodenal ulcer. Most of the duodenal ulcers were negative by x-ray but were determined by follow-up actually to be duodenal ulcers. In 20 cases the cause of the hemorrhage could not be discovered by any scientific means, even autopsy or exploratory operation, and yet subtotal gastrectomy has cured many of these cases even though the resected specimen failed to show any organic change to explain the hemorrhage.

Eugenol as a Stimulus for Gastric Mucous Secretion. F. HOLLANDER AND F. U. LAUBER. Proc. Soc. Exper. Biol. & Med., 67: 34, January, 1948.

The characteristics of gastric mucous secretion, stimulated by topical application of aqueous eugenol emulsion in several concentrations, have been investigated on 9 Heidenhain pouch dogs. The characteristics studied include: pH, viscosity, opacity, and columnar cell content. It is concluded that 5 per cent eugenol emulsion is the most effective mucagogue of all those discussed in this and previous reports. Eugenol has virtually no stimulating effect on the parietal cells. It is proposed that aqueous eugenol emulsion be adopted as a standard topical stimulating agent for further work on the physiology of gastric mucous secretion.

Famine and Food Provision in Numismatics. B. KISCH. Ciba Symposia. 9: 10, January, 1948.

The history of the coinage connected with famine and food provision from Roman times up to World War II is summarized and illustrated with numerous pictures of numismatic items related to this subject.

The Specific Heat of Human Blood. M. MENDLOWITZ. Science, 107: 97, January, 1948.

A method is described for measuring the specific heat of the cells and plasma of human blood. The specific heat of plasma was found to be 0.94 and of cells 0.77. It was also found that the specific heat of any sample of blood could be accurately calculated from the hematocrit. The lower specific heat of cells in comparison to plasma was thought to be due to their greater concentration of solids, especially iron.

Dyspareunia: A Problem for the General Practitioner. ROBERT T. FRANK. J. A. M. A., 136: 361, February, 1948.

Based on a casuistic study of 349 patients, this little considered syndrome, which causes so much marital unhappiness and disrupts so many marriages, is discussed. In nearly half of the cases, dyspareunia was the major complaint. Primary, beginning at marriage, either introital, deep or both; secondary, developing later, usually upon some local change such as shrinkage or inflammation, are noted. Nearly 20 per cent had normal pelvic findings; in them neuroses or psychoneuroses occurred in 55 per cent in contrast to women with pelvic lesions in whom psychic causes were noted in only 25 per cent. In primary and secondary dyspareunia local therapy (self intubation) and enlightenment proved effective. In psychogenic dyspareunia, caution must be exercised. The gynecologist should treat only those who want to be cured; the remainder require adequate psychiatric therapy preliminarily.

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